Mechanisms Underlying Improvements in Ejection Fraction With Carvedilol in Heart Failure

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Background—Reductions in heart rate (HR) with β-blocker therapy have been associated with improvements in ejection fraction (EF). However, the relative contributions of HR reduction, positive inotropism, afterload reduction, and reverse remodeling to improvements in EF are unknown.

Methods and Results—Twenty-nine patients (63±12 years old) with New York Heart Association class II-III heart failure underwent serial measurements of left ventricular volumes using 3-dimensional echocardiography and blood pressures by sphygmomanometry at baseline, 2 weeks, 2, 6, and 12 months after initiation of carvedilol. From these parameters, left ventricular contractility (indexed by the end-systolic pressure-volume ratio), total peripheral resistance, and effective arterial elastance (Ea) were derived. Overall, EF increased by 7-percentage points after 6 months of therapy (from 25±9 to 32±9, P<0.0001). This change was due to an increase in stroke volume (P<0.001) with no significant change in end-diastolic volume (P=0.15). The EF change correlated with increased contractility, decreased HR and decreased total peripheral resistance (P<0.003 in each case). In those patients whose EF increased at least 5 points, ~60% of the increase was due to HR reduction, ~30% was due to increased contractility, and <20% was due to the decrease in total peripheral resistance.

Conclusions—Decreased HR, improved chamber contractility and afterload reduction each contributed significantly to improved EF with carvedilol. (Circ Heart Fail. 2009;2:189-196.)

Key Words: ejection fraction □ carvedilol □ 3 dimensional echocardiography □ contractility □ heart failure □ heart rate □ vasodilation

Beta-adrenergic antagonists improve ventricular function, morbidity, and mortality in patients with chronic systolic heart failure.1–3 Heart rate reduction with β-adrenergic antagonists has been shown to be an important effect of this therapy with the magnitude of HRR being correlated with changes in cardiac function and survival effects.4–5 Additionally, chronic pacing at higher HRs in patients with heart failure has been shown to result in a lower ejection fraction (EF)7 and reversal of β-adrenergic antagonists induced HRR had deleterious effects on ventricular function, further supporting the notion that HRR is a primary mediator of their benefits.8 However, in addition to HRR, several other factors affected by β-blockers may contribute to an increase in EF, including an increase in contractility, a reduction in afterload resistance and reverse remodeling (hypertrophy regression and decreased end-diastolic volume) of the dilated left ventricle. The relative contributions of these factors to the improvement in EF, however, are unknown. In addition, the time course of the relative contributions of distinct mechanisms to the increase in EF has not been reported. The contribution of a change in afterload resistance is of particular interest during treatment with carvedilol, because this nonselective β-blocker also has vasodilating actions mediated by α1 blocking properties.9–11

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Accordingly, the purpose of this study was to determine the relative contributions of changes in HR, chamber contractility, afterload, and end-diastolic volume (reverse remodeling) to the increase in EF observed during the first 6 months of carvedilol treatment in patients with chronic heart failure. This was accomplished using a comprehensive noninvasive approach to evaluate changes in chamber and vascular properties during the initiation of carvedilol therapy and at several time points during a 1-year follow-up period.

Methods

Subjects
Twenty-nine consecutive patients with stable chronic heart failure, New York Heart Association class II or III, due to systolic dysfunction despite use of digoxin, diuretics and angiotensin converting enzyme inhibitors underwent serial 3-dimensional echocardiographic examinations before and during treatment with carvedilol. No patient had severe renal disease (creatinine >3.0 mg/dL), hepatic dysfunction (AST or ALT >3 times the upper limit of normal), severe...
pulmonary disease (FEV₁ < 1.0), recent myocardial infarction, recent (ie, <3 months) alcohol consumption, constrictive, restrictive, hypertrophic or primary valvular cardiomyopathy, or accelerated or unstable angina. Baseline systolic blood pressure was at least 85 but <150 mm Hg and resting HR was at least 60 bpm.

Carvedilol was initiated at 3.125 mg twice daily and increased weekly as tolerated toward the target dose (25 mg BID, unless weight >85 kg, then 50 mg BID). Dose titration took 49±16 days with an average of 23±11 mg/day. Sixty-two percent of subjects achieved a target dose. Other cardiac medications remained constant during the study, with the exception of diuretics, which were changed as clinically indicated. Echocardiographic measurements, HR, and arterial blood pressure (sphygmomanometry) were assessed at baseline (before carvedilol), 19±8 days, 2.2±0.6 months, 5.7±0.6 months and 13.5±0.6 months after initiating therapy, which shall correspond to time point designations of 2 week, 2 month, 6 month, and 1 year, respectively. All procedures were approved by the Columbia University Medical Center IRB, and all patients provided informed consent before enrollment.

### Three-Dimensional Echocardiography

The equipment and procedures used to perform freehand 3-dimensional echocardiography have been described previously.12–14 Multiple short axis images ≈1 cm apart, spanning from the inferior aortic valve surface to apical epicardium along with the corresponding spatial coordinates of the probe were stored for off-line analysis. The endocardial and epicardial boundaries of end-diastolic and end-systolic images were traced for 3D reconstruction of endocardial and epicardial surfaces from which end-diastolic and end-systolic chamber volumes (EDV, ESV), myocardial volumes, and myocardial mass were determined. Stroke volume (SV) was calculated as EDV-ESV and EF was calculated as SV/EDV. Left ventricular (LV) sphericity was indexed by the ratio between EDV and the volume of a sphere having the same surface area.

### Contractility

Ventricular contractility was indexed by the end-systolic pressure-volume ratio (Rₑ=Eₛ/Pₑsv/ESV)15 where the end systolic pressure $Pₑ≒SBP×0.9$.16 The advantages and limitations of using this index instead of the slope (Eₛ) and volume axis intercept (Vₑ) of the end-systolic pressure-volume relationship (ESPVR), which are more formally used to index ventricular contractility, will be discussed in detail.

### Arterial Properties and Ventricular-Vascular Coupling

Total peripheral resistance (TPR) was defined as: TPR (mm Hg/s mL)=MAP/[HR SV/60], where MAP is mean arterial pressure. Effective arterial elastance (Eₑ) is an index of arterial properties representable on the pressure-volume plane and is defined as $Eₑ=Eₛ/Pₑsv$.17 As shown previously, $Eₑ$ is related to TPR and HR: $Eₑ=kTPRHR/60$,18 where k is the proportionality coefficient between MAP and Pes. This coefficient corrects for the underestimate of the pressure at end systole by the mean arterial pressure, which for our patients was 1.18±0.08 (ie, on average, $Pₑsv=1.18MAP$).

### Statistical Analysis

The primary focus of this study was to delineate the mechanisms for the increase in EF caused by β-blocker therapy after a chronic period of drug administration (eg, 6 months). Accordingly, changes in EF after 6 months of carvedilol for the entire cohort were correlated with changes in EDV and SV, and the determinants of SV (eg, preload volume, contractility, HR, and TPR) by a Pearson’s correlation coefficient. Additionally, changes in parameters for the entire cohort, stratified by whether they did or did not exhibit a ≥5 percentage point increase in EF after 6 months of treatment, as has been done in prior studies,19–20 were evaluated by a Student t test for paired comparisons. To determine the relative contributions of HR, TPR, and $Pₑsv$ to changes in EF, multiple linear regression analysis was used. To evaluate for changes over time, 2-way repeated-measures analysis of variance was used to assess differences in the changes in parameters during therapy with carvedilol between responders and nonresponders. Time after initiation of carvedilol was considered as a within-subject factor while change in EF (responders versus nonresponders) was treated as a between subject factor. Data are presented as mean ± standard error. P values <0.05 were considered statistically significant. SAS 8.0 (Cary, NC) was used for all analyses.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

### Results

Baseline characteristics are summarized in Table 1. For all patients, EF increased by 7±7 points from baseline to the 6 month time period therapy (from 25±9 to 32±9, P<0.0001). Changes in EF were strongly correlated with changes in stroke volume (Figure 1A); but not with changes in end-diastolic volume (Figure 1B). Increased chamber contractility ($Rₑ$, decreased HR, and decreased TPR each correlated with changes in EF (Figure 1C through 1E, respectively). Because $Eₑ$ is directly related to TPR and HR, it also correlated strongly with changes in EF (Figure 1F).

Responders and nonresponders did not differ in etiology of heart failure or carvedilol dose at any time during treatment. Only a higher resting HR at baseline in responders differentiated these 2 groups (Table 2). Stroke volume increased in responders but not in nonresponders (Figure 1 and Table 2). EDV trended lower in responders and contractility, indexed by $Rₑsv$, increased more in responders (P<0.001). HR decreased in both groups, but the decrease was greater in responders (P=0.01) so that HR was comparable in both groups after 6 months. TPR did not change in responders but increased in nonresponders. $Eₑ$ decreased significantly in responders, primarily because of the decrease in HR. SV increased in responders in part because of decreases in end-systolic volume (P=0.01). Neither LV mass nor the sphericity index changed significantly in either group. Thus,
changes in HR, R_{es} and, to a lesser extent, TPR each correlated with increases in SV and EF.

The relative contribution of these factors to changes in EF was determined by multiple linear regression analysis which showed that: \( \Delta \text{EF} = 18.1 \Delta R_{es} - 0.25 \Delta \text{HR} - 0.82 \Delta \text{TPR} \) \((r^2 = 0.89)\). This relation provided a high degree of accuracy to account for changes in EF (Figure 2). Using data obtained from responders (who exhibited an average 0.18 mm Hg/mL increase of R_{es}, a 23 bpm HR reduction and a 0.14 mm Hg/s/mL reduction in TPR), the regression model indicates that 56% of the change in EF was statistically correlated with the HR reduction, 28% was correlated with the increase in R_{es} and 16% was correlated with the decrease in TPR.

Changes over time (Figure 3) show that HR decreased in both groups, but by a greater amount in responders. EDV decreased over time in responders and ESV decreased in non-responders by a greater amount in responders. EDV and 16% was correlated with the decrease in TPR. 56% of the change in EF was statistically correlated with the HR reduction, 28% was correlated with the increase in R_{es} and 16% was correlated with the decrease in TPR.

Changes over time (Figure 3) show that HR decreased in both groups, but by a greater amount in responders. EDV decreased over time in responders and ESV decreased in Table 2. Structural and Hemodynamic Parameters With Carvedilol in Responders and Nonresponders

<table>
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<th>Baseline</th>
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<th>Responders (N=17)</th>
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<th>Responders (N=17)</th>
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<td></td>
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<tr>
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<td>1.47±0.43</td>
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<tr>
<td>E_{a}, mm Hg/mL</td>
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<td>E_{a}/R_{es} ratio</td>
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<td>3.3±0.5</td>
<td>1.9±0.1†</td>
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</tbody>
</table>

Data are mean±SE.

*P<0.05 responders versus non-responders.

†P<0.05 value versus baseline by repeated measures ANOVA.
responders so that stroke volume (not shown) steadily increased. Mean arterial pressure decreased at 2 months and then returned to baseline in both groups. TPR did not change significantly, except for an increase in nonresponders at 6 months. In responders, $E_a$ decreased progressively, primarily because of the decrease in HR and $R_{es}$ increased. Ventriculo-vascular coupling ratio improved in responders. LV mass did not change significantly.

Group mean estimated pressure-volume loops were constructed using the EDV, ESV, and estimate of end-systolic pressure$^{16}$ (Figure 4). $R_{es}$ and $E_a$ are represented graphically by lines connecting the estimated end-systolic pressure-volume point to the origin or to the end-diastolic volume point on the volume axis, respectively. A comparison of these loops (paired baseline in blue, specified time of treatment in red) shows that for nonresponders, there was no significant effect at 2 weeks. At 2 months, there was a reduction in arterial pressure due to reductions in $R_{es}$ and $E_a$, the latter due primarily to a decrease in HR. Both recovered by 6 months so that there was essentially no difference from the baseline condition. The recovery of $E_a$ was due to offsetting effects of a decrease in HR and increase in TPR. In responders, $R_{es}$ increased progressively while $E_a$ decreased, mainly due to a decrease in HR; EDV trended to decline. These changes resulted in a progressive increase in stroke volume and EF with maintenance of blood pressure.

Limited data were available at 12-month follow-up (15 subjects, 5 nonresponders, and 10 responders). As at the other time points, the improvement in EF was sustained in the 6-month responders and the change in EF was correlated with

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**Figure 2.** Multiple linear regression analysis showed that changes in EF at 6 month (n=29) were correlated with changes in heart rate, $R_{es}$ and TPR (parameter values specified in the figure). The mean (solid line) and 95% CI (dotted line) of the multiple linear regression analysis is displayed. Each parameter (heart rate, $R_{es}$, and TPR) was significant at the $P<0.0001$ level.

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**Figure 3.** Change in parameters in responders (open squares) and nonresponders (closed circles) at 2 weeks, 2 months and 6 months after initiating carvedilol treatment. Data are mean±standard error. *$P<0.05$ for comparison between specified time point and baseline within specified group. Probability values for comparisons between trends over time between groups are also shown.
changes in stroke volume ($r^{2}/H_{11005}=0.69$, $P^{2}/H_{11005}=0.005$) but not with changes in EDV ($r^{2}/H_{11005}/H_{11002}=0.31$, $P^{2}/H_{11005}=0.26$). The reductions in HR and $E_{a}$, and the increase in Res were each sustained in the 6-month responders and did not change any further in nonresponders. After 12 months of therapy, LV mass declined ($250^{2}/H_{11006} \pm 17$ to $222^{2}/H_{11006} \pm 16$ g, $P^{2}/H_{11005}=0.0531$ in the entire cohort) but EDV did not change significantly ($209^{2}/H_{11006} \pm 17$ to $192^{2}/H_{11006} \pm 19$, $P^{2}=0.175$).

**Discussion**

As in prior studies,$^{9,21}$ EF increased by an average of $7\%$ percentage points within 6 months of initiating carvedilol. During this time period, a decrease in HR and an increase in contractility, indexed by $E_{es}$, were the primary factors contributing to the increase in EF. The importance of HR reduction as a mechanism for increased EF is further supported by the observation that patients whose EF increased $5\%$ points (responders) had higher baseline resting HRs and greater HR reductions than nonresponders, findings that are consistent with prior studies.$^{5,21,22}$ Reduction of TPR contributed quantitatively little to improved EF.

Prior studies of ventricular-vascular coupling have provided quantitative understanding of the dependence of EF on contractility, preload, and afterload$^{17}$ with $EF=(EDV-V_{o})/(1+E_{s}/E_{es})/EDV$. This equation, combined with our data permit estimation, on a physiological basis, of the relative contributions of the different parameters to changes in EF (see Appendix 1 in the online-only Data Supplement). One limitation in directly applying this construct, however, is that we did not measure ESPVRs; rather, we estimated a single end-systolic pressure-volume point and relied on $R_{es}$ (the end-systolic pressure-volume ratio) to quantify contractility. Although $R_{es}$ is simple to measure and has the advantage of combining changes in $E_{es}$ and/or $V_{o}$ into a single measure for assessing changes in contractility, it cannot be used directly in the equations above for EF. β-blocker enhancement of LV contractility may be manifest on the pressure-volume diagram as either an increase in $E_{es}^{23}$ or a decrease in $V_{o}^{24}$. These 2 scenarios are displayed in Figure 5, where we estimate baseline $V_{o}$ as 50 mL.$^{25,26}$ For either a constant $V_{o}$ and variable $E_{es}$ (Figure 5A) or a constant $E_{es}$ and variable $V_{o}$ (Figure 5B), the decrease in HR contributes $\approx 40\%$ and the increase in $E_{es}$ contributes $\approx 45\%$ to the increase in EF (see Appendix). Even for the case when $V_{o}$ is assumed to be 0 (so that $E_{es}=R_{es}$) the relative contributions of HR and contractility to the changes in EF are similar to the estimates above ($40\%$ and $35\%$, respectively). Thus, the conclusions using the theoretical construct are not critically dependent on an accurate choice of $V_{o}$ or whether $V_{o}$ is constant between time points. These findings confirm, on a mechanistic level, the conclusions derived based on statistical considerations of our patient data (Figure 2) that HR reduction in and of itself is a major factor contributing to increased EF during carvedilol treatment.

The impact of cardiac cycle length on ventricular-vascular coupling was derived analytically over 2 decades ago, facilitating the ability to predict the stroke volume resulting from the complex mechanical interactions between the ventricle...
and its arterial system. These findings and those of others demonstrated that HR effects ventricular-vascular coupling in a manner similar to changes in arterial resistance. This becomes evident by examining the derivation of the well established concept of indexing ventricular afterload by the effective arterial elastance (Ea). Intuitively, the influence of HR on ventricular-vascular coupling can be appreciated by realizing that at slower HRs there is more time for distal run off of arterial blood volume, thereby decreasing the pressure head against which the heart has to eject, thus an apparent reduction in afterload. Conversely, at high HRs, less time for peripheral runoff translates to higher pressure head and an apparent increase in afterload.

A meta-analysis of 35 trials, including >22,000 patients followed for an average of 9.6 months demonstrated that there was a close relation between all-cause annualized mortality and HR reduction among patients with heart failure receiving β-adrenergic antagonists and that a similarly strong correlation was observed between HR reduction and increases in EF. This suggests that HR reduction is a major contributor to the clinical benefits of β-blocker therapy in systolic heart failure. Concordant with these epidemiological findings, human data support the importance of HR reduction as a mechanism for improvements in EF with β-adrenergic antagonists. Among patients with class III heart failure and an EF < 40% who were paced >70% of the time, EF decreased with increasing HR (EF of 25 ± 6% at a HR of 90 beats per minute compared with an EF of 33 ± 6% and 30 ± 6% at 60 and 70 bpm, respectively). Additionally, a study with a similar design showed that in patients on β-adrenergic therapy, pacing at a HR of 60 bpm was associated with a 2.2 ± 5.4% increase in EF, while pacing at rate of 80 bpm was associated with a 4.5 ± 4.4% decrease in EF. These data suggest that the benefits of β-blockade on left ventricular structure and function are attenuated or reversed by increasing HR even to a modest extent.

In addition to the direct hemodynamic effects, prior studies suggest that chronic HR reduction has beneficial effects on contractility. Nagatsu et al showed that maintenance of high HR in dogs with mitral regurgitation-induced heart failure largely negated the improvement of myocardial contractility observed during chronic β-blocker therapy.

Additional evidence for the important role of HR reduction in the improvement observed in EF in patients with left ventricular systolic dysfunction can be found with newer drugs, other than β-adrenergic antagonists, that slow HR. Ivabradine, an I1 channel sinus node inhibitory agent, has been demonstrated in animals to preserve cardiac output despite the decrease in HR because of an increase in stroke volume owing to a decrease in left ventricular end-systolic diameter without modification of left ventricular end-diastolic diameter. Also, in humans, ivabradine, has been shown to significantly reduce left ventricular volumes in comparison with placebo, with a mean 5% increase in EF with ivabradine, compared with a mean 0.5% decrease in corresponding patients receiving placebo. Such an effect was acutely observed in patients with severe systolic heart failure, in whom HR reduction was accompanied by increases in stroke volume.

In the original VHeFT trial, an increase in EF of >5 from baseline at 6 months and at 1 year in the V-HeFT II trial were the strongest predictors of mortality benefit after adjusting for baseline EF. Such data have been duplicated with β-blocker therapy. Because the magnitude of HR reduction is correlated with an increase in EF with β-blocker therapy and, in our data, HR reduction was 1 of the 2 primary explanations for the observed increase in EF, HR reduction is an important goal of β-blocker therapy in patients with systolic heart failure.

Our findings are in agreement with prior studies regarding both the magnitude and time course of EF change following β-blocker initiation. The relatively long time scale over which changes occur emphasizes that they are not attributable to immediate, direct pharmacological actions but rather relate to longer term biological effects on myocyte contractile function.
improvement in EF and likely the clinical benefits of therapy. Accordingly, therapy for patients with chronic systolic heart failure should not be withheld on the basis of a low resting HR.

Although invasive measurements of LV pressure and volume provide more accurate and extensive information about systolic and diastolic LV properties than the noninvasive techniques we used, these are generally not possible in larger scale, longitudinal clinical studies. Accordingly, we could not measure ESPVRs to determine $E_a$ and $V_e$ values. Despite its limitations, $R_e$ as a single contractile index simplifies statistical assessment of contractility. Although baseline chamber and vascular properties did not differ significantly between responders and nonresponders (Table 2), end diastolic volume indexed to body size trended to be smaller in the responders than nonresponders (110±20 versus 126±60, $P=0.10$, respectively). Accordingly, it is possible that responders had heart failure for a shorter duration than nonresponders and this confounded the ability of the ventricle to reverse remodel. Unfortunately, we did not record the duration of heart failure in these subjects and thus were unable to address this limitation. Future validation of our findings using another prospectively collected data set is required to increase the certainty and generalizability of our results. Finally, in light of the small sample size, absence of data at certain time points and short follow-up as well as the inability to achieve a target dose in all patients, we cannot exclude the possibility that reverse remodeling and/or changes in TPR are more prominent and important after longer-term therapy.

In those heart failure patients whose EF increased at least 5 points, the contribution from HR reduction was twice that of increased contractility, with the decrease in TPR contributing less. These data are consistent with results of a recent meta-analysis showing that HR reduction is the major factor associated with mortality benefit. Collectively, these findings support alternate efforts to reduce HR, particularly for patients intolerant to $\beta$-blocker therapy or for those whose HR does not decrease adequately in response to $\beta$-blockers.

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Disclosures

Dr Sackner-Bernstein served as a consultant to GlaxoSmithKline during the planning, execution, and analysis of this study.

References


**CLINICAL PERSPECTIVE**

β-adrenergic antagonists are a mainstay of pharmacological therapy for patients with chronic systolic heart failure. Heart rate reduction with β-adrenergic antagonists has been shown to be an important effect of this therapy with the magnitude of heart rate reduction being correlated with changes in ejection fraction (EF). However, the relative contributions of other factors affected by β-blockers to increases in EF, including an increase in contractility, a reduction in afterload resistance and reverse remodeling (hypertrophy regression and decreased end-diastolic volume) of the dilated left ventricle in addition to heart rate reduction are not known. In this study, 29 subjects with systolic heart failure underwent serial measures of chamber and vascular properties using 3-dimensional echocardiography and blood pressures by sphygmomanometry at baseline, 2 weeks, 2, and 12 months after initiation of carvedilol. The increase in EF (7 percentage points) after 6 months of therapy correlated with increased contractility, decreased heart rate (HR), and decreased total peripheral resistance and among those patients whose EF increased at least 5 points, ~60% of the increase was due to HR reduction, ~30% was due to increased contractility and <20% was due to the decrease in total peripheral resistance. These data suggest that mechanistically, HR reduction is a major factor contributing to the increase in EF with carvedilol therapy. This suggests that efforts to find alternate means of reducing HR can be fruitful, particularly for patients intolerant to β-blocker therapy or for those whom HR does not decrease adequately in response to β-blockers.
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SUPPLEMENTAL MATERIALS
APPENDIX 1

The relative contributions of changes in HR, TPR, $E_{es}$ and $V_o$ to changes in EF ($\Delta EF$) can be estimated analytically from the equation:

\[
EF = \frac{(EDV-V_o)/(1+Ea/Ees)}{EDV}.  \tag{1}
\]

If baseline parameter values are denoted by the subscript “B” and parameter values at a specified follow-up time point are specified by the subscript “F”, it follows that:

\[
EF_B = \frac{(EDV_B-V_{o,b})/(1+TPR_{B,H}B/1000/E_{es,B})}{EDV_B}
\]
\[
EF_F = \frac{(EDV_F-V_{o,f})/(1+TPR_{F,H}F/1000/E_{es,F})}{EDV_F}
\]

so that,

\[
\Delta EF = EF_F - EF_B.
\]

The contribution of the change of a particular parameter to an observed $\Delta EF$ can be determined by calculating $\Delta EF$ assuming all parameters remain at their baseline values except for the parameter of interest. For example, $\Delta EF$ expected for a specified change in HR ($\Delta EF_{HR}$) can be estimated by calculating EF at baseline ($EF_B$) and the EF expected when all parameters remain at their baseline value except HR ($EF_{F,HR}$):

\[
EF_B = \frac{(EDV_B-V_{o,b})/(1+TPR_{B,H}B/1000/E_{es,B})}{EDV_B}
\]
\[
EF_{F,HR} = \frac{(EDV_B-V_{o,b})/(1+TPR_{B,H}F/1000/E_{es,B})}{EDV_B}
\]

\[
\Delta EF_{HR} = EF_{F,HR} - EF_B
\]

The relative contribution of HR change ($Q_{HR}$) can then be estimated by comparing the actual change in EF to the change expected in response only to HR:

\[
Q_{HR} = (\Delta EF - \Delta EF_{HR})/ \Delta EF
\]

This procedure can be repeated for any parameter of interest.