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ARTICLE

Model-based meta-analysis of changes in circulatory system physiology in patients with chronic heart failure

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Abstract

To characterize and compare various medicines for chronic heart failure (CHF), changes in circulatory physiological parameter during pharmacotherapy were investigated by a model-based meta-analysis (MBMA) of circulatory physiology. The clinical data from 61 studies mostly in patients with heart failure with reduced ejection fraction (HFrEF), reporting changes in heart rate, blood pressure, or ventricular volumes after treatment with carvedilol, metoprolol, bisoprolol, bucindolol, enalapril, aliskiren, or felodipine, were analyzed. Seven cardiac and vasculature function indices were estimated without invasive measurements using models based on appropriate assumptions, and their correlations with the mortality were assessed. Estimated myocardial oxygen consumption, a cardiac load index, correlated excellently with the mortality at 3, 6, and 12 months after treatment initiation, and it explained differences in mortality across the different medications. The analysis based on the present models were reasonably consistent with the hypothesis that the treatment of HFrEF with various medications is due to effectively reducing the cardiac load. Assessment of circulatory physiological parameters by using MBMA would be insightful for quantitative understanding of CHF treatment.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
In clinical studies of chronic heart failure (CHF), important physiological indices, such as cardiac load, could not be assessed without invasive measurements.

WHAT QUESTION DID THIS STUDY ADDRESS?
Cardiac and vasculature indices, including cardiac load, were estimated from clinical studies with various medications in CHF by using a new type of model-based meta-analysis (MBMA).

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
The reductions on a cardiac load index, myocardial oxygen consumption estimated by MBMA, reasonably correlated with the decrease in odds ratio of mortality of patients with heart failure with reduced ejection fraction.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

Assessment of circulatory physiological parameters by using MBMA would be beneficial for quantitative understanding of CHF treatment.

INTRODUCTION

In chronic heart failure (CHF), the blood supply to the body is insufficient, thus feed-back mechanisms, such as the sympathetic nervous and renin-angiotensin systems, are often overactive.[1] This further overloads the heart and causes it to become exhausted. There may be an increased risk of an events occurring if the heart is continuously under heavy loads compared to its capacity; reduction of the cardiac loads is considered necessary for recovery from CHF. CHF is classified principally in heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). In the former, EF is less than 40%, but in the latter, it is 40 to 50% or more. In reality, however, CHF includes even more diverse groups of patients, each of whom requires an appropriate treatment.

Current treatment guidelines (2017 American College of Cardiology Foundation/American Heart Association [ACCF/AHA] Guideline[1] and European Society of Cardiology [ESC] Guidelines[2]) primarily recommend the use of β-blocker together[3–5] with angiotensin-converting enzyme (ACE) inhibitor[6] or angiotensin II receptor blocker (ARB) or angiotensin receptor neprilysin inhibitor (ARNI) for patients with HFrEF. In addition, diuretics are used widely for those who have peripheral edema (e.g., swelling of legs). So-called guideline-directed management and therapy (GDMT) β-blockers include carvedilol, bisoprolol, and sustained-release metoprolol. Bisoprolol and metoprolol selectively block β_1 receptor, and carvedilol blocks α_1, β_1, and β_2 receptors. On the other hand, bucindolol, which blocks β receptors nonselectively, and short-acting metoprolol tartrate are not recommended because of insufficient efficacy. Reduction in mortality was observed in patients with sinus rhythm by treatments with β-blocker, but not with atrial fibrillation in an umbrella review and meta-analytic assessment.[7] Calcium channel blocker (CCB) and direct renin inhibitor (DRI) were not effective for CHF treatment but the reason is not fully understood. In patients with HFpEF, no pharmacotherapy has improved the mortality whereas diuretics show some beneficial effects.

To compare these therapeutic agents and to understand the pathology of CHF, evaluations of clinical changes in the circulatory system's physiological parameters, including cardiac function indices (cardiac output [CO], EF, end-systolic elastance [E_{es}], or maximum elastance), cardiac load indices (myocardial oxygen [MVO_2] consumption or myocardial volume oxygen, and effective arterial elastance [E_a]), and vasculature indices (total peripheral vascular resistance [TPR] and total arterial compliance [TAC]) would be important.[8] CO and EF have been routinely used for the diagnosis of CHF. MVO_2 is proportional to the energy consumption by the heart and should be a good marker of cardiac load theoretically. However, some of these indices, such as E_{es}, E_a, and MVO_2 have not been evaluated in most clinical trials since the measurements are invasive. Instead, heart rate (HR) and B-type natriuretic peptide are evaluated often in clinical trials because they correlate with the prognosis for some medications,[9,10] although they cannot explain therapeutic effects for all the medications. On the other hand, in the field of circulatory physiology, various parameters described above have been related mathematically to HR, blood pressure, and ventricular volume.[11] Therefore, it may be possible to estimate them based on carefully constructed models.

Current efficacious medicines, β-blockers, and ACE inhibitors exert an initial effect on the circulatory system, which causes direct changes in HR and blood pressure, and, in addition, they may have secondary therapeutic effects to the heart. In the sympathetic nervous system, β-blockers improve β-receptor density and suppress G protein uncoupling, which are decreased by long-term catecholamine stimulation.[12,13] In addition, β-blockers improve heart contraction and reduced circulating levels of vasoconstrictor substances, such as norepinephrine, renin, and endothelin. It has been considered that these changes may be associated with delays in the progression of myocardial injury.[14,15] ACE inhibitors act on the renin-angiotensin-aldosterone (RAA) and kallikrein-kinin systems and reduce blood pressure. In the myocardium, ACE inhibitors may also delay cardiac remodeling by reducing oxidative stress.[16] However, the clinical significance of these secondary effects of β-blockers and ACE inhibitors are unknown.

In this study, to characterize and compare various medicines for CHF, we collected noninvasive observations of HR, blood pressure, and left ventricular volume during CHF treatment from clinical trials of β-blockers, ACE inhibitors, DRI, and CCB. The goal of this study is to apply mathematical models of circulatory system physiology to these data in order to understand the progression of treatment of CHF quantitatively, and in particular to find a good indicator of mortality odds ratio. To our knowledge, this is the first report

of mechanism-oriented model-based meta-analysis (MBMA) of circulatory system physiology.

METHODS

Selection of drugs

β-blockers (carvedilol, metoprolol, bisoprolol, and bucindolol), ACE inhibitor (enalapril), DRI (aliskiren), or CCB (felodipine) were selected because odds ratio of mortality compared to the control group (β-blockers) or placebo group (other drugs) were obtained.

Data collection of odds ratios of mortality

The inclusion and exclusion criteria of the trials used in this study were listed in Table 1a,b, respectively. The number of trials and subjects for each drug are described in Table S1 and detailed background characteristics and the reference of each trial are described in Table S2. For β-blockers, the results of network meta-analysis reported by Chatterjee et al. were used.[17] For enalapril, aliskiren, and felodipine, odds ratio of mortality was extracted from the literature.

Data collection of clinical parameters

The inclusion and exclusion criteria of the trials, the number of trials and subjects for each drug, and detailed background characteristics and the reference of each study were similarly listed in Table 1c,d, Tables S1 and S3, respectively. The means and SDs or standard errors of systolic arterial blood pressure (SAP), mean blood pressure (MAP), HR, end-systolic volume (ESV) and end-diastolic volume (EDV) at baseline and 3, 6, and 12 months after treatment initiation were extracted from the literature. It should be noted that, considering the inclusion criteria for both mortality and clinical parameter collection, the target population of this study was mostly patients with HFrEF, but a relatively small number of borderline patients were also included. In addition, as stated in the footnote of Table 1, all the searches were conducted in 2014, so trials of recently developed drugs, such as ARNI, were not included.

Correction of between-trial heterogeneity and meta-analysis

To correct the between-trial heterogeneity, multiple regression analyses were performed on baseline values and 3-, 6-, and 12-month changes (only for β-blockers) in each

TABLE 1 Inclusion and exclusion criteria of studies[a]

(a) Inclusion criteria of studies for collection of mortality[b,c]

ID	Criteria
1	Controlled randomized clinical trial in patients of heart failure with reduced ejection fraction, and reported mortality.
2	The average baseline EF was 45% or less.
3	The average NYHA class was 1.8–3.2.

(b) Exclusion criteria of studies for collection of mortality[b]

ID	Criteria
1	Non-randomized clinical trial.
2	Number of patients was <100.
3	A follow-up period of less than three months.
4	The average age of the drug was more than 70.

(c) Inclusion criteria of studies for collection of clinical parameters[d]

ID	Criteria
1	Double or single blinded open trials in patients of chronic heart failure with reduced ejection fraction.
2	The average baseline EF was 45% or less.
3	The average NYHA class was 1.8–3.2.
4	The average baseline HR was 70–90 bpm.
5	The average baseline systolic blood pressure was 100– 140 mm Hg.

(d) Exclusion criteria of studies for collection of clinical parameters

ID	Criteria
1	Trials in patients with dyssynchrony, or severe angina pectoris.
2	Trials in patients with hepatic, renal impairment, or receiving dialysis.
3	Trials in patients with a history of myocardial infarction or bypass surgery within 2 months (patients with acute heart failure).
4	Trials in patients with defibrillation devices.

[a]The searches were conducted in 2014, so trials conducted after that date were not included.

[b]The criteria are principally conformed those adopted in a network meta-analysis reported by Chatterjee S et al.

[c]The search formula: "name of drug" [all fields] (ACE inhibitor: enalapril, captopril, lisinopril, angiotensin II receptor blocker: candesartan, valsartan, losartan, β-blocker: carvedilol, metoprolol, bisoprolol, bucindolol, atenolol, nebivolol, DRI: aliskiren, CCB: felodipine, amlodipine) AND "heart failure" [all fields] AND ("odds ratio" [all fields] OR "risk ratio" [all fields] OR "hazard ratio" [all fields] OR "mortality" [all fields]).

[d]The search formula: "name of drug" [all fields] (ACE inhibitor: enalapril, captopril, lisinopril, angiotensin II receptor blocker: candesartan, valsartan, losartan, β-blocker: carvedilol, metoprolol, bisoprolol, bucindolol, atenolol, nebivolol, DRI: aliskiren, CCB: felodipine, amlodipine) AND "heart failure" [all fields] AND ("pressure" [all fields] OR "heart rate" [all fields] OR "end-diastolic diameter" [all fields] OR "end-diastolic volume"[all fields]), Filter activated by "Humans".

of the observed parameters (SAP, MAP, HR, ESV, and EDV). Potential covariates included age, New York Heart Association (NYHA) class, proportions of men and patients with ischemic heart failure, treatment duration, baselines of each parameter, and β-blocker used. The stepwise forward selection based on Akaike Information Criterion was performed to select the statistically significant covariates, and multicollinearity between variable factors was evaluated using variance inflation factor (VIF). Based on the results of multiple regression analyses, the baselines and changes for each parameter were corrected to be the values when all identified covariates were the mean of the studies for odds ratios of mortality in each drug class.

The mean values of the corrected parameters and their standard errors at 3, 6, and 12 months after treatment initiation were calculated with a random-effects model (DerSimonian Laird method, R 3.5.2).[18]

Calculation of parameters of circulatory system physiology

If the MAP was not described but SAP and diastolic arterial pressure (DAP) were described, MAP (mm Hg) was conventionally estimated by Equation 1.

$$\mathrm{MAP} = \mathrm{DAP} + \frac{\mathrm{SAP} - \mathrm{DAP}}{3} \tag{1}$$

If the ESV or EDV was not described but end-systolic diameter (ESD) or end-diastolic diameter (EDD; cm) was described, the ESV or EDV (ml) was estimated by Equations 2 and 3 (Teichholz method).

$$\mathrm{ESV} = \frac{7.0 \times \mathrm{ESD}^3}{2.4 + \mathrm{ESD}} \tag{2}$$

$$\mathrm{EDV} = \frac{7.0 \times \mathrm{EDD}^3}{2.4 + \mathrm{EDD}} \tag{3}$$

The left ventricular volume was expressed in ml/m^2 assuming that body surface area is 1.7 m^2 for a body weight of 60 kg and height of 170 cm.

Stroke volume (SV; ml) to EDV, CO (L/min), and EF (%) were calculated from the following Equations 4 to 6.

$$\mathrm{SV} = \mathrm{EDV} - \mathrm{ESV} \tag{4}$$

$$\mathrm{CO} = \mathrm{SV} \times \mathrm{HR} \tag{5}$$

$$\mathrm{EF} = \frac{\mathrm{SV}}{\mathrm{EDV}} \tag{6}$$

Based on the cardiac mathematical models, cardiac function indices, cardiac load indices, and vasculature indices were calculated from the mean values of observed parameters (Figure 1a). E_{es} is the maximum elastance at the end of systole, and is the slope of the end systolic pressure-volume relationship (ESPVR; Figure 1b). E_{es} is considered to be an index of the cardiac contraction force. Sunagawa et al. and Schwartzenberg et al. reported that E_{es} can be calculated simply as a ratio of end-systolic pressure

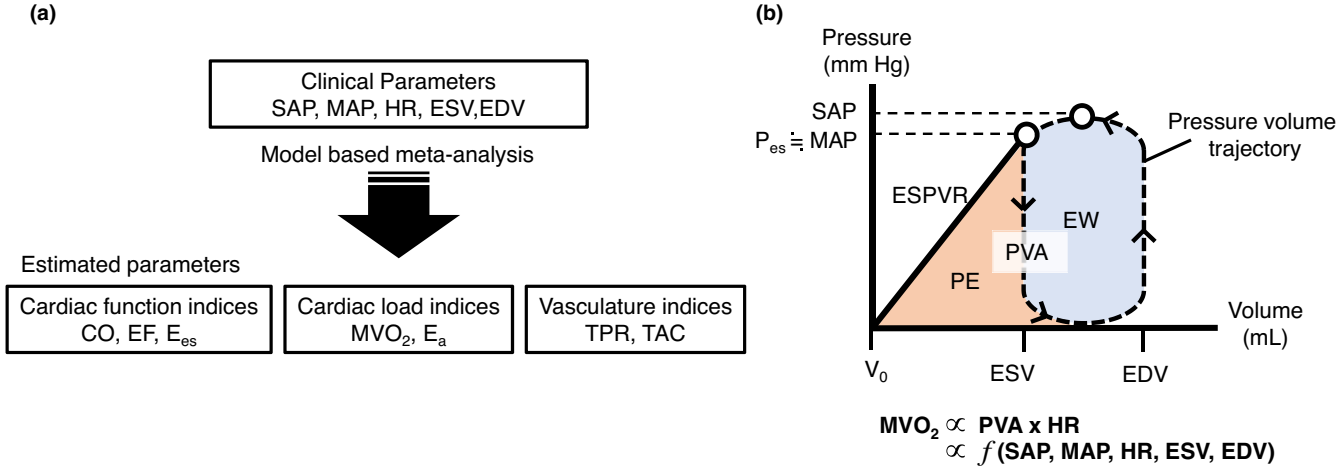

FIGURE 1 Overview of this study (a) and pressure-volume relationship in left ventricle (b). CO, cardiac output; E_a, effective arterial elastance; EDV, end-diastolic volume; E_{es}, end-systolic elastance; EF, ejection fraction; ESPVR, end systolic pressure-volume relationship; ESV, end-systolic volume; EW, extra work (energy required to pump blood); HR, heart rate; MAP, mean blood pressure; MVO_2, myocardial oxygen consumption; PE, potential energy (energy required for the basic metabolism and contraction of the heart); P_{es}, end-systolic pressure; PVA, pressure-volume area (consumption energy consumed per heartbeat); SAP, systolic arterial blood pressure; TAC, total arterial compliance; TPR, total peripheral vascular resistance

(P_{es}) to ESV by assuming V_0 (the volume axis intercept, where left ventricular pressure is zero) ≈ 0.[19,20] P_{es} was approximated by MAP in this study. This approximation was discussed in detail by Shigemi et al.[11] and although estimated P_{es} itself would be varied widely among individuals, the accuracy of E_{es}/E_a are considered to be high enough for clinical use. E_{es} (mm Hg/ml) was estimated by Equation 7.

$$E_{es} = \frac{P_{es}}{ESV} \approx \frac{MAP}{ESV} \tag{7}$$

E_a is the total amount of resistive and pulsatile afterload derived from the ventricular pressure-volume relationship,[19] and is calculated by the ratio of P_{es} to SV.[21] E_a (mm Hg/ml) was estimated from Equation 8.

$$E_a = \frac{P_{es}}{SV} \approx \frac{MAP}{SV} = TPR \times HR \tag{8}$$

The pressure-volume area (PVA) links hemodynamic factors to MVO_2 and corresponds to the total automatic energy in one beat[22,23] (Figure 1b). This is based on the physics concept that the product of pressure and volume change is equivalent to energy. In the ventricular pressure-volume relationship, PVA is the sum of the area surrounded by the trajectory of the left ventricle pressure and the left ventricle volume while the heart beats once (extra work) and the area surrounded by ESPVR and the pressure-volume trajectory (potential energy). PVA correlates with myocardial oxygen consumption.[8,23] PVA is approximated as the sum of the area of a right angle triangle (with base ESV and height PVA) and a trapezoid (with base SAP, top PVA and height [EDV-ESV]) from Figure 1b assuming that $V_0 \approx 0$, $P_{es} \approx$ MAP,[11] the left ventricular maximum pressure ≈ SAP. PVA as consumption energy (J/min/m^2) per beat was estimated with Equation 9. The constant term is for unit conversion.

$$PVA = 1.33333 \cdot 10^{-4} \cdot \left(\frac{MAP \cdot ESV}{2} + \frac{(SAP + MAP) \cdot (EDV - ESV)}{2} \right) \tag{9}$$

MVO_2 (J/min/m^2) was estimated using Equation 10, which was obtained from the correlation between PVA and MVO_2 in table 2 of the report by Takaoka et al.[24] A detailed explanation of the derivation of this equation was described in the Supplement.

$$MVO_2 = \left[2.42 \cdot PVA + \left\{ 0.4 \cdot \left(E_{es} - 2.4 \right) + 0.017 \right\} \right] \cdot HR \tag{10}$$

TPR (dynes·s/cm^5) was estimated by Equation 11 approximating venous pressure to 0 where 1 mm Hg/L/min =79.98 dynes·sec/cm^8.[23]

$$TPR = \frac{(MAP - CVP)}{CO} \times 79.98 \tag{11}$$

where CVP represents the central venous pressure, which was considered negligible compared to MAP. TAC (mL/mm Hg) is an index of blood vessel compliance and was estimated by the ratio of the difference between SAP and DAP to SV.[25]

$$TAC = \frac{SV}{(SAP - DAP)} \tag{12}$$

$$TAC = \frac{(EDV - ESV)}{\frac{3}{2} \times (SAP - MAP)} \tag{13}$$

Standard errors were calculated based on the propagation rule of error. All data analyses were conducted using R version 3.5.2.

RESULTS

Data characteristics

Based on the selection criteria, 61 eligible studies were identified in which the circulatory parameters (SAP, MAP, HR, ESV, or EDV) were evaluated. Detailed background characteristics of each study are described in Tables S2 and S3. Significant covariates on the baseline and the treatment effects of observed circulatory parameters for β-blockers are shown in Tables S4 and S5. The average EF values were considerably less than 40% for all the trials.

Treatment effects on blood pressure, heart rate, and left ventricle volume

Figure 2 shows the integrated mean changes in observed circulatory parameters after treatment. Both SAP and MAP were decreased by the ACE inhibitor, DRI, and CCB. Regarding β-blockers, SAP and MAP were decreased by carvedilol and bisoprolol, and transiently decreased by metoprolol, but not by bucindolol. HR was clearly decreased by β-blockers (carvedilol, metoprolol, bisoprolol, and bucindolol) whereas no change was observed with the other drugs. Decreases in HR were consistent for all β-blockers and for the entire treatment period of 12 months. ESV and EDV were decreased most efficiently by β-blockers,

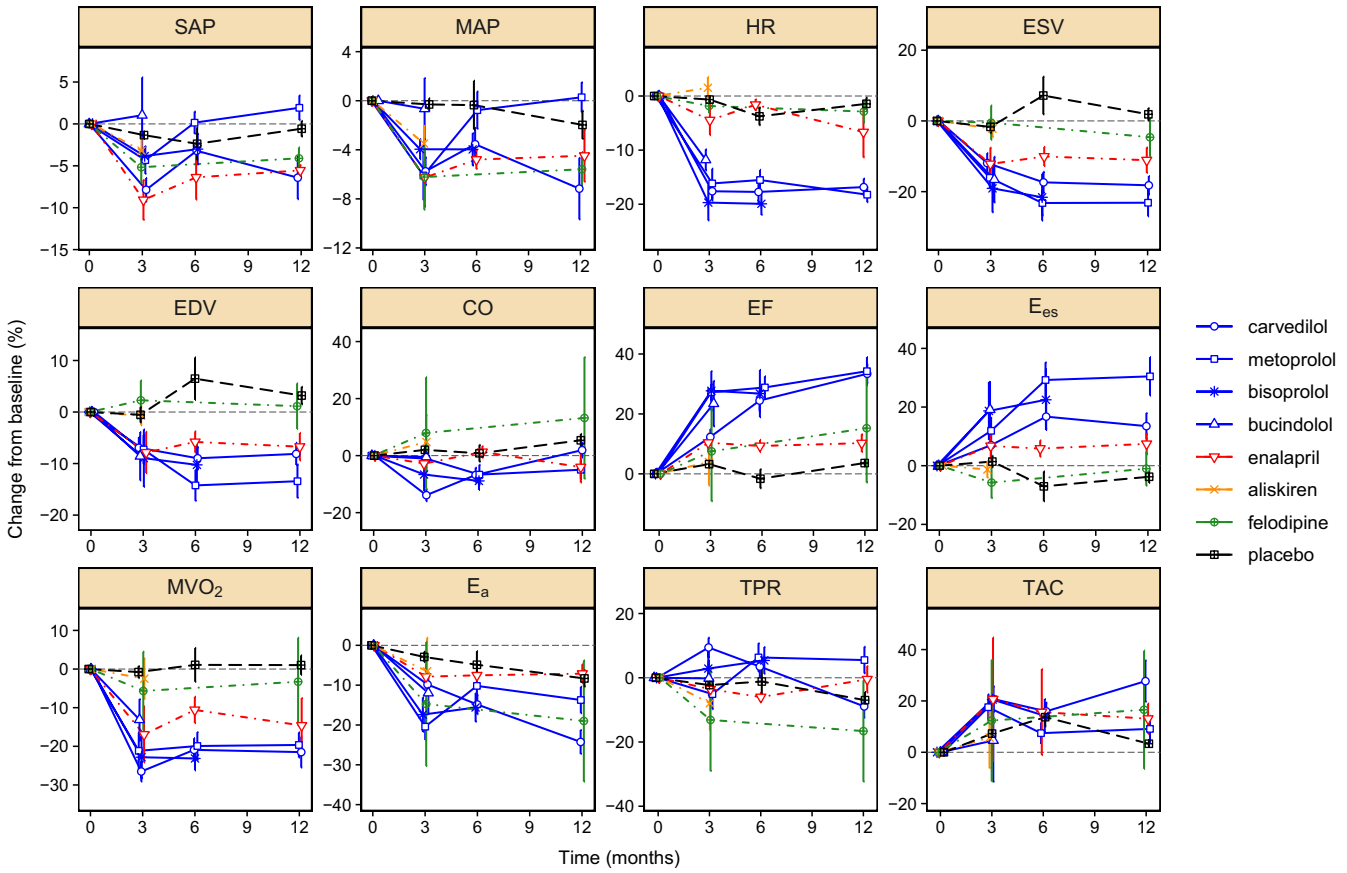

FIGURE 2 Estimated time-course changes of circulatory physiological parameter after treatment initiation. Data represent mean change ratio and relative standard error of the change. By multiple regression analysis, the variable factors for the baseline and the change ratio (in β-blocker group) were identified and corrected. The corrected results of 61 trials were integrated by meta-analysis based on the random effects model (DerSimonian Laird method). The mean change ratio of function indices (CO, EF, E_{es}), cardiac load indices (MVO_2, E_a), and vasculature indices (TPR, TAC) were estimated by hemodynamic mathematical model. The standard error was calculated based on the error propagation. CO, cardiac output; E_a, effective arterial elastance; EDV, end-diastolic volume; E_{es}, end-systolic elastance; EF, ejection fraction; ESPVR, end systolic pressure-volume relationship; ESV, end-systolic volume; EW, extra work (energy required to pump blood); HR, heart rate; MAP, mean blood pressure; MVO_2, myocardial oxygen consumption; PE, potential energy (energy required for the basic metabolism and contraction of the heart); P_{es}, end-systolic pressure; PVA, pressure-volume area (consumption energy consumed per heartbeat); SAP, systolic arterial blood pressure; TAC, total arterial compliance; TPR, total peripheral vascular resistance

followed by the ACE inhibitor. ESV and EDV were not changed by DRI and CCB.

Treatment effects on estimated cardiac function indices

Estimated CO was decreased by carvedilol, metoprolol and bisoprolol within 6 months, in line with the general class effect of β-blockers.[26] On the other hand, estimated CO was not changed by bucindolol, ACE inhibitor, DRI, and CCB at 3 months. Estimated EF was continuously improved by β-blockers and reached a 30% increase at 12 months. ACE inhibitor and CCB improved estimated EF and reached a 10% and 15% increase at 12 months, respectively. DRI exerted almost no change compared to the control group. Estimated E_{es} was improved by the β-blockers and the ACE inhibitor, but no difference was observed in DRI and CCB.

Treatment effects on estimated cardiac load indices

Regarding β-blockers, estimated MVO_2 was decreased by more than 20% by carvedilol, metoprolol, and bisoprolol, and 13% by bucindolol at 3 months. Decreases in estimated MVO_2 by β-blockers were stable for 12 months. Estimated MVO_2 was decreased 17% by ACE inhibitors at 3 months. With DRI and CCB, almost no change was observed compared with the control group. Estimated E_a showed a tendency to decrease with β-blockers and CCB, but was not changed by ACE inhibitors and DRI.

Treatment effects on estimated vasculature indices

Estimated TPR was markedly decreased by CCB, which is consistent with the reported class effect.[27] On the other hand, β-blockers were prone to increase estimated TPR. No difference was observed with ACE inhibitor and DRI. Estimated TAC was increased by carvedilol, with a change ratio of 28% at 12 months. No clear change was observed with other drugs compared to the control group.

Relationships between odds ratio of mortality and cardiac indices

Figures 3 and 4 show the correlations between the observed and estimated changes in circulatory physiological parameters and the odds ratio of mortality. Estimated MVO_2 was highly correlated with the odds ratio of mortality regardless of the time point (R^2: 0.89 [3 months], 0.90 [6 months] and 0.86 [12 months]). The R^2 values of HR at 3, 6, and 12 months were relatively high (0.79, 0.71, and 0.82, respectively) but less than those of estimated MVO_2. With regard to the estimated CO, the correlation was similar to that of estimated MVO_2 ($R^2 = 0.88$) at 3 months, but was less evident at 6 and 12 months (0.70 and 0.48, respectively). Correlations for all the parameters at 6 and 12 months are shown in Figure S1.

DISCUSSION

Assumptions of this study

In this study, parameters of the circulatory system physiology were estimated based on information generally available from clinical trials, avoiding necessity of invasive measurements.

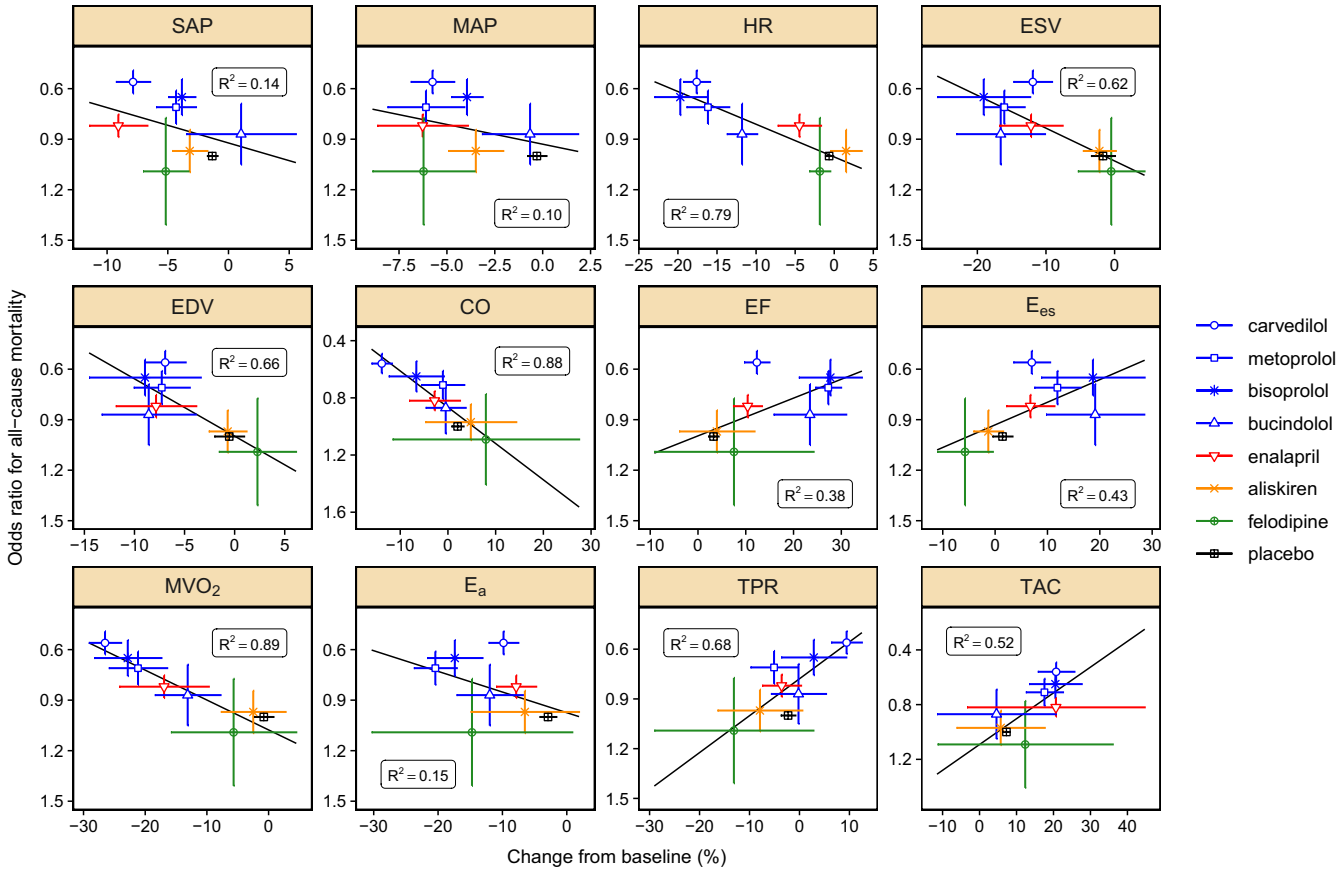

FIGURE 3 Correlations between change of circulatory physiological parameter and odds ratio of mortality after 3 months from treatment initiation. The horizontal axis represents mean change percent and relative standard error from the baseline, and the vertical axis represents mean and standard error of odds ratio. The correlation between mean change ratios of clinical parameters (SAP, MAP, HR, ESV, and EDV) and estimated indices (CO, EF, E_{es}, MVO_2, E_a, TPR, and TAC) integrated by meta-analysis from 61 trials, and the mean odds ratios of mortality obtained from 21 large-scale clinical trials was represented. CO, cardiac output; E_a, effective arterial elastance; EDV, end-diastolic volume; E_{es}, end-systolic elastance; EF, ejection fraction; ESPVR, end systolic pressure-volume relationship; ESV, end-systolic volume; EW, extra work (energy required to pump blood); HR, heart rate; MAP, mean blood pressure; MVO_2, myocardial oxygen consumption; PE, potential energy (energy required for the basic metabolism and contraction of the heart); P_{es}, end-systolic pressure; PVA, pressure-volume area (consumption energy consumed per heartbeat); SAP, systolic arterial blood pressure; TAC, total arterial compliance; TPR, total peripheral vascular resistance

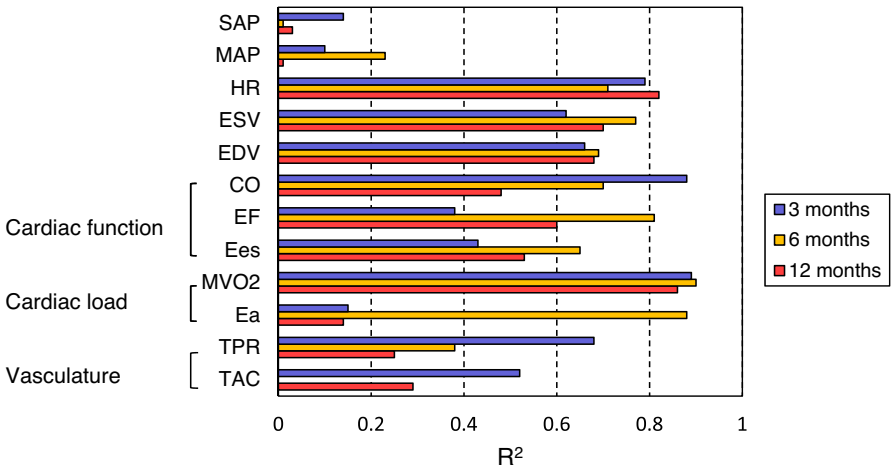

FIGURE 4 Determination coefficients between circulatory physiological parameters and odds ratio of mortality after 3, 6, and 12 months from treatment initiation. Determination coefficients (R^2) between clinical parameters (SAP, MAP, HR, ESV, EDV) and estimated indices (CO, EF, E_{es}, MVO_2, E_a, TPR, TAC), and odds ratio of mortality at 3, 6, and 12 months were represented. Blue, orange and red bars represent R^2 at 3, 6, and 12 months, respectively. CO, cardiac output; E_a, effective arterial elastance; EDV, end-diastolic volume; E_{es}, end-systolic elastance; EF, ejection fraction; ESPVR, end systolic pressure-volume relationship; ESV, end-systolic volume; EW, extra work (energy required to pump blood); HR, heart rate; MAP, mean blood pressure; MVO_2, myocardial oxygen consumption; PE, potential energy (energy required for the basic metabolism and contraction of the heart); P_{es}, end-systolic pressure; PVA, pressure-volume area (consumption energy consumed per heartbeat); SAP, systolic arterial blood pressure; TAC, total arterial compliance; TPR, total peripheral vascular resistance

For this purpose, several assumptions were made including $P_{es} \approx$ MAP, $V_0 \approx 0$, and the left ventricular maximum pressure ≈ SAP. In addition, we adopted the observed correlation for the relationship between MVO_2 and PVA in one particular study. All of these are based on some theories or circumstantial evidences[11,19–25] but have not been fully validated yet. Errors may occur between the true and approximate values. However, because the above assumptions were made for all drugs in the same way, the relative changes (e.g., EF improves with beta-blockers, ACE, and CCBs, in that order) are considered reliable. Another important assumption for calculating MVO_2 is that all the energy is being used for the beating of the heart. It assumes that the energy used is transferred from the heart to the bloodstream and surrounding tissues. However, if the heart is using energy for its own recovery, metabolism, or secretion, there will be errors in the estimation.

In order to obtain reliable results from the MBMA analysis, the backgrounds of the trials should be homologous, as required in the meta-analysis. To correct for heterogeneity between trials, multiple regression analysis was performed for clinical parameters using various covariates as described in the Method section. Moreover, because CHF is heterogenous, it may be necessary to account for differences in diverse types of systolic heart failure, including idiopathic, hypertensive, and valvular origin. However, these were not fully included in the analysis because of incomplete description in some manuscripts. These covariates, as well as other covariates not included in this analysis may have affected the accuracy of MBMA if there were notable differences between trials.

Effects of each medication on prognosis

An interesting finding of this research is that the reductions on MVO_2 estimated by MBMA from many studies in patients with HFrEF correlated reasonably with the decrease in odds ratio of mortality. The β-blockers reduce HR and ventricular volume, and ACE inhibitors reduce ventricular volume and pressure. Considering estimation method of MVO_2, it could be an excellent cardiac load marker, summing up pulsatile load, volume load, and pressure load. The hypothesis that reduction in cardiac load is important for the treatment of CHF is widely known, the present analysis is valuable in that it showed that the results of many studies with various medications were consistent with the hypothesis.

Changes in estimated MVO_2 were in line with differences in the effectiveness between β-blockers included in this study. These differences were considered to ascribe to the differences in the changes in HR and blood pressure between β-blockers. Consistent with previous findings, most β-blockers markedly reduced HR, however, bucindolol only led to a weak reduction. Blood pressure was clearly decreased by carvedilol and bisoprolol, whereas the effect of the other β-blockers was transient or insignificant. Some differences between β-blockers can be explained by the inhibitory action of carvedilol via α-receptor and by the high selectivity to the β_1 receptor of bisoprolol.[28] However, the reasons why bucindolol showed reduced effects on HR and blood pressure are unknown.

The transient decrease in estimated CO following carvedilol treatment leads to reduction of cardiac load,

however, it may simultaneously worsen the quality of life of patients. The decrease in estimated CO was less evident in the other β-blockers. On the other hand, improvements in estimated E_{es} consistently continued until 6 months with all β-blockers, suggesting that this is a more time-consuming process of the recovery of cardiac function compared with immediate decreases in HR and MVO_2. The improvement in estimated E_{es} with metoprolol was better than that with carvedilol at 12 months. On the other hand, E_a at 6 and 12 months is lower for carvedilol than for metoprolol, resulting in little difference between two drugs in E_{es}/E_a which represents the efficiency of left ventricular contraction that pumps blood through the arteries.[11] For carvedilol, changes in MAP, CO, EF, E_a, and TPR were continuous through 12 months.

Blood pressure was effectively reduced by ACE inhibitors in this analysis, as shown in previous studies.[2] Estimated MVO_2 was reduced by ACE inhibitors but to a weaker degree than β-blockers. Increases in estimated E_{es} and EF with treatment were also less noticeable with ACE inhibitors. Although further research is necessary to confirm the relationship between cardiac sympathetic nerve activity and changes in estimated E_{es} and EF, a difference may exist in the progression of reverse remodeling during treatments with β-blockers and ACE inhibitors.

Calcium channel blocker acts as a vasodilator, as indicated by the reduced estimated TPR and blood pressure. However, it did not decrease the cardiac load itself. The effects of CCB or DRI were evaluated in addition to the standard treatment, mostly with an ACE inhibitor, in the clinical trials analyzed in this study. Thus, analyzing the effects of CCB or DRI monotherapy on blood pressure or estimated MVO_2 is not possible in this study. In the ESC Guidelines,[2] CCB and DRI are not recommended as routine treatment for patients with heart failure with reduced ejection fraction as there is insufficient evidence on clinical outcome.

Following recommendations in the 2017 ACCF/AHA Guideline,[1] β-blockers and ACE inhibitors are the most frequently used medicines for the pharmacological treatment of patients with HFrEF at ACCF/AHA stage C (i.e., NYHA II and III). Among β-blockers, carvedilol, bisoprolol, and sustained-release metoprolol are considered to be effective in reducing the risk of death, whereas bucindolol is considered to lack stable effectiveness across different populations. In the present study, the odds ratios of mortality were consistent with the recommendations and evidence described in the current treatment guidelines. This is reasonable because the clinical trial for odds ratio used in this study was partly the same as the studies on which the recommended therapy guidelines are based on.[3,4,6,29–31]

Contrary to the present analysis, Kaye et al. reported that MVO_2 was not significantly changed by carvedilol treatment within 3 months in patients with CHF.[32] MVO_2 was measured directly by an invasive method in this study, unlike our analysis. Because ESV and EDV were not described in the report by Kaye et al. we calculated them from cardiac output and left ventricular ejection fraction (LVEF) described, and estimated MVO_2 by our method for comparison. MVO_2 was reduced by 25% which was consistent with the 27% reduction obtained in our MBMA analysis for carvedilol. There were some ambiguities in this analysis. The estimated ESV and EDV were somewhat larger than usual, and the blood pressure was not decreased in Kaye's study, which was slightly deviated from the general observations in carvedilol treatments. Even so, if this analysis is correct, there is a discrepancy between the oxygen consumption calculated from the work by the beating and the oxygen consumption actually measured from the oxygen concentration in the blood. Given the conservation of energy, the heart may be consuming energy for some untraceable activities. Although further studies are obviously warranted to clarify this issue, MBMA seems to have provided a new perspective for understanding cardiac load and CHF treatment.

In this study, changes in circulatory system physiology as well as changes in blood pressure, HR, and left ventricular volume during CHF treatments were reasonably illustrated by analyses based on the numerous observations in clinical studies. Results of the present analysis can be useful to understand treatment of HFrEF, because of overall consistency. The interest in MBMA has increasing, mainly in the drug development field because it enables an objective and efficient evaluation of new drug candidates. The present study indicates that MBMA is also useful to compare various treatments and to understand their mechanisms of action.

Limitations

There are several limitations to this study. First, many parameters were estimated based on the theory of circulatory system physiology and therefore, validation with more direct (but invasive) methods would be needed. In particular, more comparisons with MVO_2 by assessing O_2 and CO_2 concentrations in the blood near the heart would be needed. In addition, assessments of E_{es} and E_a are important. Second, it is difficult to estimate class effects for ACE inhibitor, CCB, and DRI because the number of analyzed drugs for these groups was insufficient. Furthermore, HF being a complex clinical syndrome with large phenotypic heterogeneity, the results of this study would be potentially inappropriate for some types of patients. Last, it should be noted that all the analysis is retrospective. In the future, prospective evaluations of the circulatory system physiology are necessary to fully validate the present study.

CONCLUSIONS

The results of this study showed that MVO_2 estimated by MBMA was reasonably correlated with the odds ratio for mortality at 3, 6, and 12 months during the treatment of HFrEF, indicating that the MBMA analysis can provide insightful information, such as capturing quantitative prognosis of the complicated disease. MBMA should therefore be more extensively utilized in the analysis of various diseases in the future to gain knowledge for optimizing pharmacotherapy.

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CONFLICT OF INTEREST

Y.S. is an employee of Sanofi K.K. However, Sanofi K.K. is not involved in this analysis. S.G. was involved in this study before she joined Astellas Pharma Inc. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

R.T., Y.S., and A.H. wrote the manuscript. R.T., H. Sato, H. Suzuki, and A.H. designed the research. R.T., S.G., H.Y., and A.H. performed the research. R.T., Y.S., S.G., and H.Y. analyzed the data.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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