Effects of sauna bath on heart failure: A systematic review and meta-analysis

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Abstract

Aim: To determine the cardiovascular effects of sauna bath on heart failure patients. **Methods and results:** PubMed, Cochrane Library and CINAHL databases were searched to identify randomized and non-randomized controlled studies to compare effects of sauna bath with no sauna bath. Studies were searched for both infrared sauna bath and Finnish sauna bath. The strength of evidence was rated using a modified GRADE approach. Out of 1,444 studies, nine met the inclusion criteria and were included in this review. Seven of these nine studies were included in the meta-analysis, which included a total of 491 patients with heart failure (>95% in New York Health Association (NYHA) class II-III), and with mean ejection fraction of <40% at baseline. Only studies with infrared sauna bath met the inclusion criteria. In the meta-analysis, exposure to an infrared sauna bath in 60° C for 15 minutes, followed by a 30-minute rest in warm environment, 5 times a week for 2-4 weeks, was associated with a significant reduction in B-type natriuretic peptide (BNP), cardiothoracic ratio (CTR) and an improvement in left ventricular ejection fraction (EF). There was no significant effect on left ventricular end-diastolic diameter, left atrial diameter, systolic blood pressure or diastolic blood pressure. The strength of evidence varied from moderate to insufficient. **Conclusion:** Infrared sauna bath was associated with short-term improvement in cardiac function. More evidence is needed about long-term effects of sauna bath and the effects of a Finnish sauna on cardiovascular health among patients with heart failure or other cardiovascular diseases.

Keywords: Heart failure, sauna bath, waon therapy.

Introduction

The prevalence of heart failure (HF) is increasing at the same time as treatment strategies are improving and the mean age of death from HF has risen. [1, 2] Aging of the population, worsening risk factor profile and improved treatments and diagnostic technology have led to an increase in the prevalence of HF. [3-5] This suggests that there will be an increase in the number of patients with HF in the more advanced stages of the disease. HF is associated with high morbidity and mortality and will impose a significant economic burden on health care systems in the future. [6]Thus, beyond pharmacologic and other relatively expensive interventional therapies, e.g. cardiac resynchronization therapy, it will be important to search for additional possible strategies to manage the symptoms of these patients. Although several established cardiovascular disease risk factors such as hypertension, diabetes, and history of coronary heart disease explain a large proportion of the risk of HF, its pathogenesis is still not fully understood, as several other factors appear to be involved. Multidisciplinary and easily applicable treatment strategies should be focused on improving the quality of life of HF patients, and therefore the value of life-style factors such as exercise training and sauna bathing among HF patients should be further investigated. [7]

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The access to saunas in many parts of the world, along with the relatively low cost of sauna bathing, gives it a great potential as a lifestyle treatment modality. It is therefore important to summarize the evidence and identify gaps of knowledge that can help suggest paths of future study and potential for clinical application.

The aim of this study was to assemble the evidence through a systematic review and meta-analysis of the effects of sauna bath in patients with HF, evaluated by symptoms, blood pressures, biomarkers, cardiac dimensions and function, endothelial function and mortality.

Methods

Search strategy

The search strategy was based on the PICO approach (Population, Intervention, Control, Outcome) recommended by the Cochrane Handbook for Systematic reviews. [8] We searched the databases of PubMed [9], Cochrane library [10] and CINAHL [11] with search terms "sauna", "saunas", "steam bath", "steam baths" and "waon therapy". The aim was to identify all literature of the health effects of sauna bath on cardiovascular effects. The studies with cardiovascular effects were reviewed in more detail, including reference lists, to identify the studies that met the inclusion criteria. The searches were done during 2016-02-02 to 2016-0419, with a final updated search 2017-04-27 identifying one additional study.

Inclusion criteria

The search results were independentlyreviewed by two authors (MK and HH). Studies with abstract in English were included.

Studies that met the following criteria were included in the review: 1) Randomized and non-randomized controlled studies. 2) Population (P): Heart failure, men and women, ≥16 years of age. 3) Types of sauna bath (I=Intervention): moist (>10% relative humidity), dry (0–10% relative humidity) or infrared. Temperature of sauna bath: 60–100 degrees Celsius. 4) Sauna bath compared to no sauna bath. (C = control) Studies comparing different types of sauna baths were excluded. 5) Types of outcome measures (O = Outcome):
I) Symptoms and signs: New York Heath Association (NYHA) class, systolic blood pressure
(SBP), diastolic blood pressure (DBP); II) Blood biomarkers: B-type natriuretic peptide (BNP); III) Imaging: left atrial diameter (LAD), left ventricular end diastolic diameter (LVEDD), left ventricle ejection fraction (EF), cardiothoracic ratio (CTR), endothelial function. IV) Mortality; V) safety/tolerance.

Assessment of study quality

The quality assessment of the randomized and non-randomized observational studies was done using the Downs and Black checklist.[12] The last point (27) was modified to “did the study report a power calculation?” with points given as: no = 0; yes, power ≥70% = 1 point, ≥75% = 2 points, ≥80% = 3 points, ≥85% = 4 points and ≥90% = 5 points. Thus, the maximum score for quality assessment was 32. Total points by study are displayed in table 1.

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The quality of the studies was broadly divided into 3 categories: 0–10 low, 11–21 moderate, 22–32 high. This scale was not included in the original article.[12]

Data synthesis and analysis

Studies that met the inclusion criteria and were similar in follow-up length and study design were pooled to conclude a meta-analysis. The criteria for inclusion in the meta-analysis were not pre-specified and were formed after the search results. For continuous data, mean differences between the groups and standard deviations of the change were used and presented as random effects 95% confidence intervals in forest plots. The data was constructed with the statistical software RevMan 5.3. [13, 14]

Few of the studies that met the inclusion criteria reported the differences of the means or the standard deviations of the changes. In accordance with Cochrane Handbook for Systematic Reviews of Interventions, standard deviation of the change for each outcome was calculated by using the p-values and sample sizes. In studies reporting the p-value as ($p<x$), the upper limit (x) was used as the p-value. In studies not reporting p-values for all outcomes, we imputed the standard deviations for changes from baseline according to Cochrane Handbook of Systematic Reviews. [8] This was done by calculating the correlation coefficient for both the treatment and control measurements, and the mean of those values was used for the matching outcome. The difference had to be <0.25, values and the mean coefficient >0.5, otherwise the coefficient was not used. The coefficients were calculated from Tei 2016, Kihara 2002, Kuwahata 2011 and Miyata 2008 studies. Standard errors were transformed to standard deviations. As neither means nor standard deviations for BNP results were presented for the studies by Ichiki 2017 and Tei 2016 (interpreted to have the same data), the authors of the Ichiki 2017 study were contacted, and they provided us with the means and standard deviations of changes for the BNP.

Statistical tests for variance were also done with the RevMan 5.3 software. [13] Chi^2 statistic was used as a test for heterogeneity and I^2 statistic was used to quantify heterogeneity. Statistical heterogeneity was observed in varying degrees. As the outcomes still came basically from the same studies, all outcomes were reported with the random effects model. Narrative synthesis was used with outcomes that were found in only one study (endothelial function, mortality) and for the results that were retrieved from the studies that weren't included in the meta-analysis (Basford 2009).

The statistical analysis was done by two authors (MK and LB).

Quality of the evidence

To summarize the quality and strength of the evidence in support of the intervention, we used a modified version of the GRADE (The Grades of Recommendation, Assessment,
Development, and Evaluation) approach. [8] The quality of evidence was rated with a scale of 4 to 1 as following: 4=high, 3=moderate, 2=low and 1=insufficient. The assessment was modified so that the quality of evidence of a group of studies could be reduced by: 1) Moderate risk for bias (total points 11-21, reduces by 1) and high risk for bias (total points 010) reduces by 2); 2) Inconsistency/heterogeneity (significant heterogeneity = I2≥50%, reduces by 1); 3) Indirectness (if interventions of interest were directly applied to the population of interest) [15], reduces 1 if not; 4) Imprecision (mean not in favor, CI95% not totally in favor of intervention, both reduce by 1); 5) Publication bias (reduces by 1).

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Results

Of the 1,444 studies, 553 studied the health effects of sauna bath. A full-text review of those studies identified 145 studies on cardiovascular effects of sauna bath. These studies were chosen as possibly eligible and checked for identification of additional records from the reference lists. A deeper review of these studies resulted in the identification of nine studies that fulfilled the inclusion criteria. A list of included studies and patient characteristics is presented in Table 1. Of those studies, seven were included in the meta-analysis. Two studies, Kihara 2009 and Basford 2009, were excluded from the meta-analysis because of different follow-up period, outcome measure and study design compared to the other included studies.

In the meta-analysis, the seven studies reported a total of 491 patients with HF, 275 in the sauna groups, 216 in the control groups. All the seven studies evaluated an infrared sauna therapy (Waon therapy). The frequency of sauna bath was 5 times a week and the follow-up periods varied from 2 to 4 weeks. The severity of HF according to the NYHA classification varied from grade II to IV at baseline, though the majority of patients (>95%) were classed II or III. The mean EF at baseline was found to be <40% in all of the studies included. As our search strategy produced a large number of records to be reviewed by full text, we haven't provided a full list of excluded records.

Of the seven studies included in the meta-analysis, six were randomized. The risk for bias for each of the included studies (total points) was rated moderate by our modified version of the Downs and Black checklist.

Risk for bias in studies included

Generally, the risk of bias in the included studies was considered moderate on a scale of 0–32 points, each of the studies scoring in the moderate region (11–21 total points). (Table 1). Tei 2016 reported 73 and 73 patients at baseline but in the results we could only see 73 and 69 patients (BNP), 71 and 66 (NYHA) and 71 and 69 (CTR). No source of funding was reported for any of the studies.

Effects of interventions

Symptoms and signs Blood pressure

Six studies in the meta-analysis assessed the effects of sauna bath on SBP (mmHg). There was no significant effect of sauna bath compared to control (mean difference (MD) -2.58, 95% confidence interval [CI95%]: -5.86–0.70, I^2 =42%, P=0.12).

Five studies in the meta-analysis reported effects of sauna bath on DBP (mmHg). There was no significant effect of sauna bath compared to control group (MD=1.42; CI95%: -3.89–1.05, I^2=27%, P=0.26).

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NYHA class

Four studies reported NYHA classifications at baseline and at the end of the follow-up. Three of them were reported as number of patients in each class. One study reported NYHA class as means with standard deviations. There were some improvements in the NYHA classifications of the patients in the sauna groups compared to the controls. No studies were included in the meta-analysis, as none of the studies reported the criteria used to judge NYHA class.

Blood biomarkers BNP

Five studies reported effects on BNP (pg/ml). Sauna bath lowered the BNP value significantly in the sauna group in comparison with the control group. (MD= -124.62; CI95%= -198.09– (-51.14), I^2=37%, P=0.0009).

The different assays for measuring BNP in the five studies are listed in table 2.

Imaging

Left atrial and ventricular diameter

Four studies reported effects on LAD (millimeters, mm) and LVEDD (mm) measured by echocardiography. There was no significant difference between sauna bath and control in LAD (MD=-0.32; CI95%: -1.51–0.88, I^2=25%, p=0.60) or LVEDD (MD=-1.07; CI95%: 2.20–0.07, I^2=58%, P=0.07).

EF

Six studies reported the effects of sauna bath on EF (%), which was significantly higher in patients with sauna intervention compared to controls (MD=1.45; CI95%: 0.55–2.35, I^2=0%, P=0.002).

CTR

Six studies reported the effects on CTR (= ratio of maximal horizontal cardiac diameter to maximal horizontal thoracic diameter on x-ray). Sauna bathing lowered the CTR significantly in comparison to control. (MD=-1.82, CI95%= -2.54– (-1.09), I^2=31%, P<0.00001).

Endothelial function

One non-randomized crossover study (Kihara 2002) reported changes in endothelial function in vessel percent flow-mediated dilation and percent nitroglycerin, which was defined as “the percent change in diameter between 4 min after administration of sublingual nitroglycerin spray (300 μg) and that on the initial scan.” Flow mediated dilation improved in the treatment group from baseline 4.4 (+-2.5) to 5.7 (+-2.5) p = 0.0006. There was no significant difference in the control group. The NTG-induced (Nitroglycerin-induced) dilation change from baseline to after sauna was not different in any of the groups.

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Mortality

One study [16] reported mortality as a part of cardiac events during a 5-year follow-up of sauna bathing (Waon therapy) versus only standard medical treatment. The patients were compared to a control group matched for age, sex and etiology and severity of HF. The study population was 129 patients admitted to a Japanese hospital, of which 64 patients were treated daily with for 5 days after admission, and Waon therapy was continued at least twice a week in an outpatient clinic after hospital discharge. A cardiac event was defined as cardiac death or rehospitalization due to HF. The cardiac event rate was 68,7% in the control group and 31,3% in the sauna bathing group. The authors calculated a 38% reduction of cardiac events by sauna bathing.

Safety/tolerance

Two studies reported adverse events. Tei 2016 reported 7 Waon therapy-related minor adverse events: decrease in blood pressure, hypovolemia, increase in urine volume, decrease in body weight, and bleeding after tooth extraction. In the Basford 2009 study no adverse events were observed.

Quality of evidence

The quality of evidence was rated moderate to insufficient. There was moderate evidence for an effect on BNP, EF, and CTR, low evidence for outcomes SBP, DBP and LAD and insufficient evidence for LVEDD. The results of the assessment are presented in Table 4.

Discussion

This was a comprehensive systematic review, which resulted in a meta-analysis of seven studies including 491 patients with HF. In all of the seven studies, the patients received infrared sauna bath, called Waon therapy, in 60 degrees Celsius for 15 minutes followed by a 30-minute rest in warm environment, 5 times a week, for 2 to 4 weeks. Out of seven outcomes, three (EF, BNP, CTR) showed significance in favour of sauna bath compared to control patients (no sauna). All patients were receiving standard medications according to the original publications.

The quality of evidence varied from moderate to insufficient. The main factors that reduced the quality were risk for bias and imprecision. This means that the evidence presented by this review does support a therapeutic effect of sauna bathing on HF, and more studies are thus needed to be able to draw definitive conclusions.

Two of the studies included observed adverse effects and reported only minor adverse effect, which might mean that sauna bath is a safe activity for this group of cardiac patients. Notably, this systematic review was not designed to assess the general safety of sauna bathing among HF patients. A possible source for identification of additional studies on safety could be inclusion of studies with other languages than English.

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We could observe that no single parameter was consequently followed in all of the 7 studies in the meta-analysis. Only the outcome LVEDD showed heterogeneity over the set limit (I^2>50%) to affect the strength of evidence. We could observe that if the Kihara 2004 study was removed, which led to reduced heterogeneity, the outcome still did not show significance. Removing Kihara 2004 from other outcomes did not change the significance of the result in any of the outcomes.

NYHA class was assessed in four of the studies included, but none of those presented the methods they used to differentiate between classes. According to previous studies, NYHA class has a high level of inter-observer variability, especially in discriminating NYHA class II and III, in which most of the patients in this review were rated. [17] Thus we refrained from separate analyses of NYHA class II and III.

A recent systematic review from Brazil only identified five studies on Waon therapy for patients with HF and showed favorable effects on natriuretic peptides and blood pressure. [18] No significant difference in blood pressure was seen in our analysis including two additional studies, instead a significant difference in EF was found. These difference in results are most likely explained by our wider search strategy resulting in 1,444 compared to 247 identified studies, and 554 compared to 10 full-text reviews, respectively, in this study compared to that of the Brazilian study.

Interestingly, only Waon therapy studies were included in our study but not any other sauna bath studies including Finnish sauna bath. In 1991, Dr. Tei originally started the first pilot chronic sauna study, which is now called Waon therapy, for HF patients. [19] The sauna temperature of Waon therapy was set at 60° C which was a lower temperature than general sauna or Finnish sauna. It was given for 15 min followed by 30-min rest in warm environment so as not to cause any side effects on HF patients and performed 5 times per week for several weeks.

The possible beneficial mechanistic pathways of sauna bathing have been discussed in a recent systematic review by Laukkanen et al. [20] Possible underlying mechanisms on vascular function listed in the review are reduction in systemic blood pressure, improvement in endothelial function, reduction in oxidative stressand inflammation, beneficial modulation of the autonomic nervous system, positive alteration in levels of circulating vascular risk factors such as natriuretic peptidesand lipids, hormonal changes; improved vascular function and improvement in the, cardiorespiratory systemas well as cardiovascular function. A response to a sauna bath has been compared to physical activity such as walking, which has, as mentioned in the introduction, found to improve the quality of life and heart failure related hospitalization in patients with systolic heart failure.[7]

Limitations

As the majority of patients had EF < 40% in all studies in the meta-analysis the results are primarily applicable for patients with HF and reduced EF. Different effects in HF patients with a preserved EF could be expected as studies have shown that these patients react differently to medical therapies and have a different pathophysiology. [21, 22]

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The follow-up of the studies in the meta-analysis was relatively short, with a mean duration of 2–4 weeks. Therefore, more studies with longer follow-up are needed to provide evidence of the long-term cardiac effects.

The studies included in the meta-analysis were interpreted to have been conducted by partly the same research groups, which must also be taken into consideration when interpreting the data.

Accurate statistical tests were not presented appropriately in every study. This might lower the accuracy of a portion of the results. We also included both randomized and non-randomized studies, which could be assumed to lower the scientific confidence of the results in this review. However, the only non-randomized study didn't influence the results enough to affect the quality of evidence.

As only studies with infrared sauna baths met the inclusion criteria, this review cannot show any definite supporting evidence of a positive value of Finnish sauna bathing on HF patients, although Finnish sauna might have physiological effects similar to those of an infrared sauna that operates with a lower temperature.

The BNP levels were measured with different types of assays (table 2) in the analyzed studies, and two of the studies did not report the manufacturer of the assay used. This might affect the accuracy of the BNP analysis.

Conclusions

This study shows that infrared sauna bath was associated with short-term improvement in cardiac function among patients with HF. There is moderate evidence that infrared sauna bath improves EF and decreases BNP levels and cardiac size. However, data of effects of sauna bath on SBP, DBP, LAD are limited without consistent evidence on the relationship between sauna bath and adaptations in LVEDD. The results of this review highlight the paucity of well-designed large long-term studies of intermittent heat exposure, in particular Finnish saunas, in patients with HF.

Figure legends

Figure 1: Flow chart.

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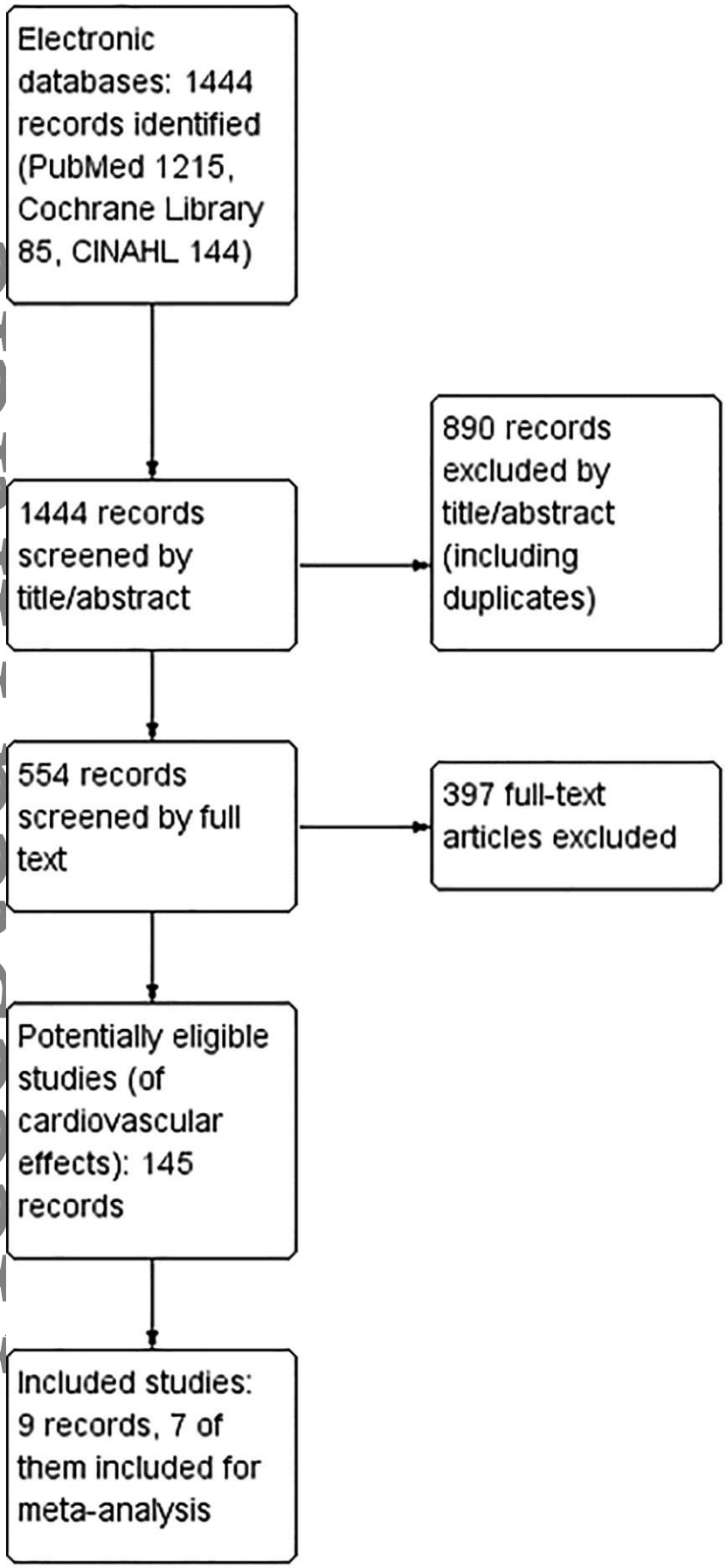

utcomes systolic blood
ter (LAD) and left ventricular

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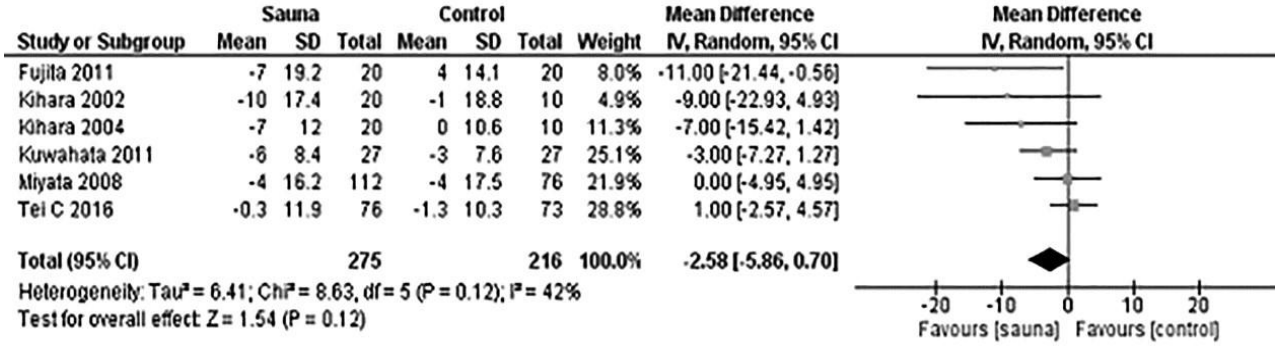

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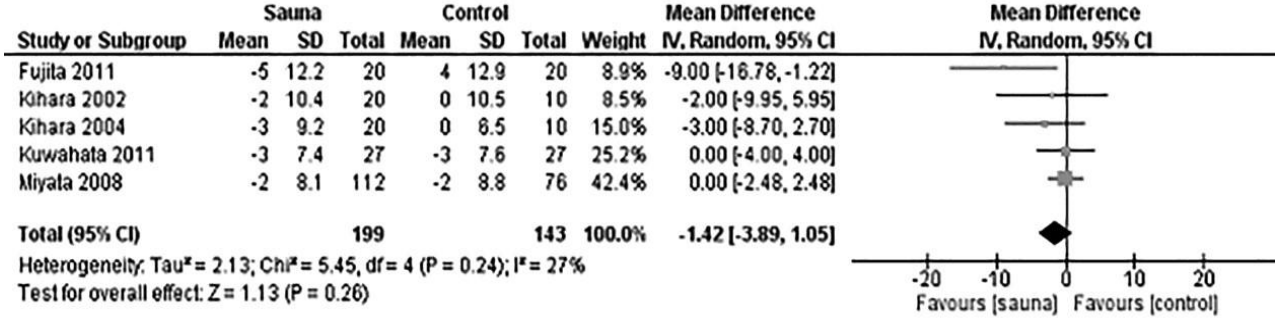
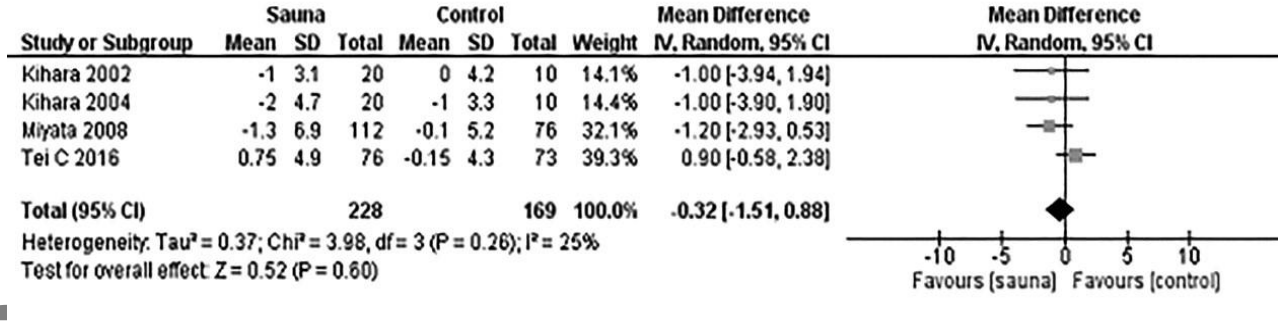
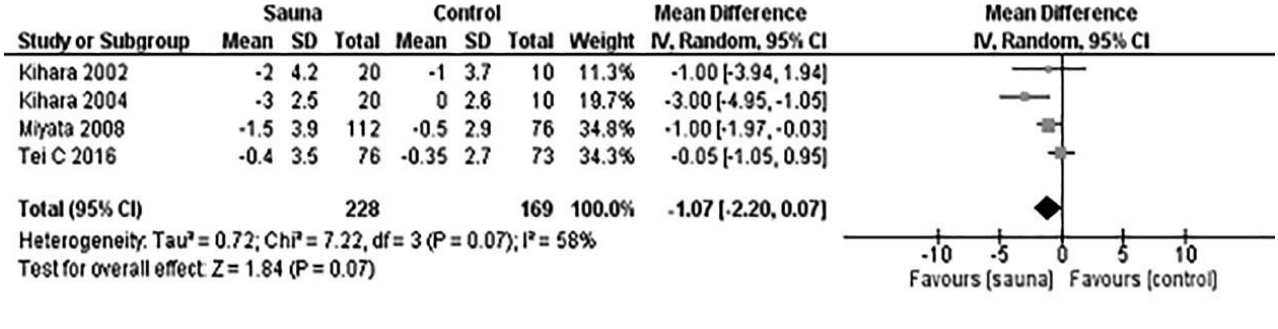


DBP



LAD



LVEDD

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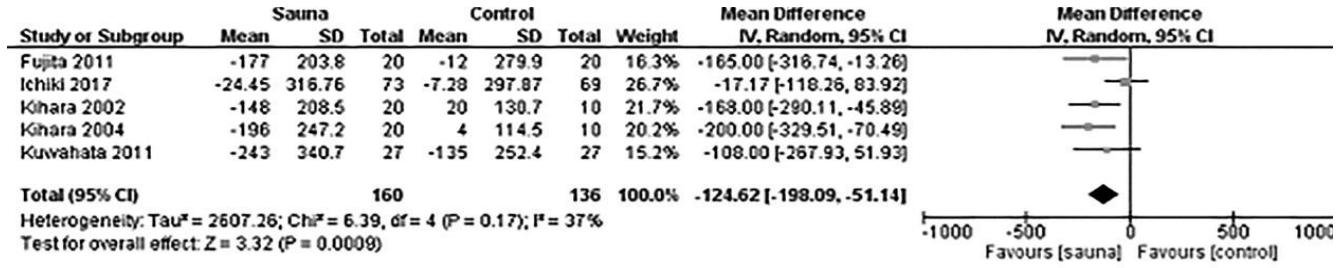
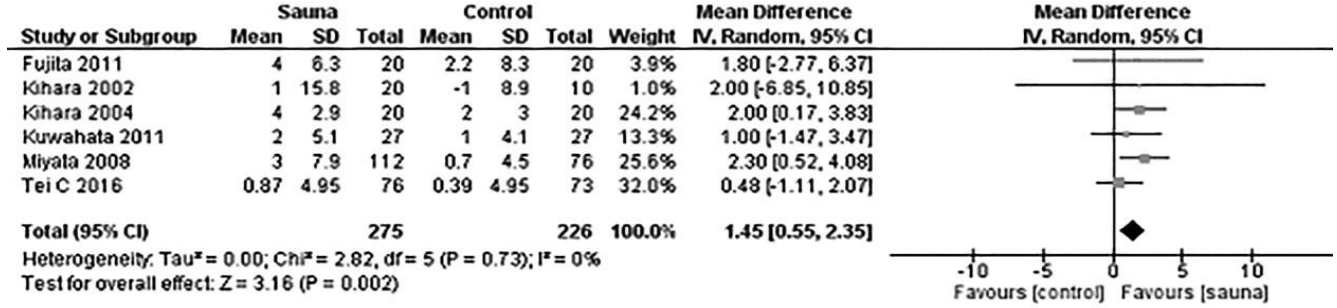
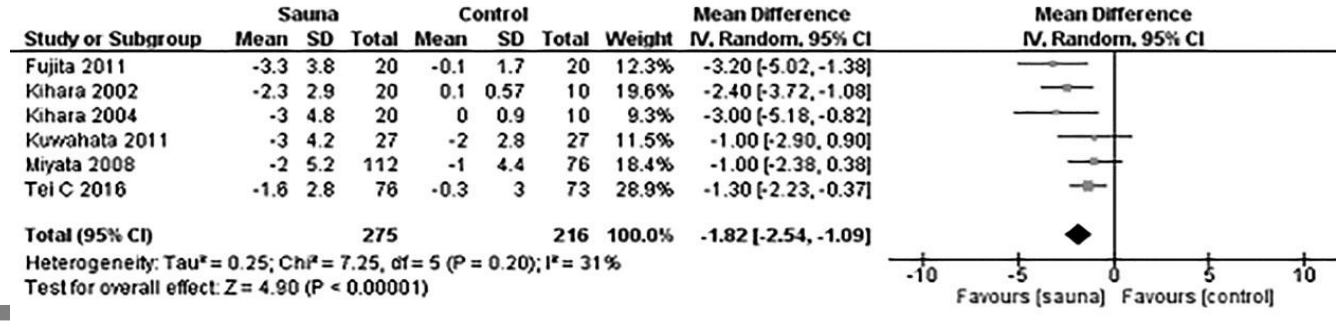
Figure 3: Forest plots of the results of the meta-analysis for the outcomes B-type natriuretic peptide (BNP), left ventricular ejection fraction (EF) and cardiothoracic ratio (CTR).



BNP



EF



CTR

Funding

No

Conflict of interest

No

Appendices

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Table A1: Quality assessment results.

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Effects of vasodilation in heart failure with preserved or reduced ejection fraction implications of distinct pathophysiologies on response to therapy. *Journal of the American College of Cardiology*. 2012; 59: 442-51.

Tables

Table 1: List of studies included and patient characteristics.

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Study	Study design, blinding	Number of participants (sauna / control)	NYHA classes at baseline for all groups. If numerical = at average	Mean ejection fraction: sauna / control	Mean age: sauna / control	Male %	Ischemic cardiomyopathy (sauna / control, % of respective group)	Medications, % of sauna / control ACE-inhibitors or (ACE-I) Angiotensine II receptroblockers (ARB)	B-blockers	Diuretics	Implantable cardioverterdefibrilator, cardiac resynchronisation therapy-device (% of sauna / control)	Location	Quality assesment: Downs and Black score (of 32)
Kihara 2002 [25]	Controlled trial, no	20 / 10	II, III	38 / 32	62 / 64	60	15 / unknown	"All patients"	"Most patients"	"All patients"	Not listed	Japan	16
Kihara 2004 [26]	Randomized controlled trial (RCT), no	20 / 10	II, III	29 / 29	59 / 59	70	20 / 20	95 / 90	55 / 40	95 / 100	Not listed	Japan	19
Miyata 2008 [27]	RCT, no	112 / 76	2.61, 2.51	31.6 / 36.6	63 / 66	66	15 / 9	Data not available	Data not available	Data not available	Not listed	Japan	20
Kihara 2009 [18]	Retrospective study, no	64 / 65	2.6	38.5 / 35.8	61.9 / 64.6	64	26 / 21	69 / 65	61 / 57	73 / 83	Not listed	Japan	19
Kuwahata 2011 [28]	RCT, no	27 / 27	II, III, IV	31 / 33	63 / 64	70	37 / 37	ACE-I 52 / 63 ARB 48 / 37	93 / 93	100 / 100	-	Japan	19
Fujita 2011 [29]	RCT, no	20 / 20	II, III	31.8 / 34.3	64 / 65	83	30 / 35	100 / 95	90 / 95	not listed	-	Japan	19
Tei 2016 [30]	RCT, no	76 / 73	II, III, IV	30.2 / 30.9	66 / 66	61	26 / 30	ACE-I 58 / 55 ARB 24 / 27	86 / 88	97 / 99	CRT-P 1 / 4 CRT-D 18 / 22, ICD 2 / 4	Japan	21
Ichiki 2017 [31] (substudy of Tei 2016)	RCT, no	76 / 73	II, III, IV	30.2 / 30.9	66 / 66	61	26 / 30	ACE-I 58 / 55 ARB 24 / 27	86 / 88	97 / 99	CRT-P 1/ 4 CRT-D 18 / 22, ICD 2 / 4	Japan	21
Basford 2009 [32]	Crossover, no	9 - crossover	II, III, IV	20	72	67	Not listed	Not listed	Not listed	Not listed	Excluded from the study	USA	-

Table 2: BNP assays reported in the studies.

Study	Source	Reported BNP assay type
Fujita 2011	Plasma	Chemiluminescent enzyme immunoassay using a commercially available kit (PATHFAST, Mitsubishi Chemical Medience Co, Ltd, Tokyo, Japan)
Kuwahata 2011	Plasma	Chemiluminescent enzyme immunoassay using a commercially available kit (Pathfast, Mitsubishi Chemical Medience Co., Ltd., Tokyo, Japan)
Kihara 2002	Plasma	Radioimmunoassay
Kihara 2004	Plasma	Radioimmunoassay

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Ichiki 2017	Plasma (EDTA)	2-site immunoenzymatic sandwich assay on a Beckman Coulter DXI 800 (Beckman Coulter, Inc., USA)

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Table 3: Types of intervention and schedule of exposure in the studies included.

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Study	Type of sauna	Temperature	Duration of single sauna bath	Frequency	Followup(s)

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Kihara 2002	Far-infrared-ray dry sauna	60°C	15 min	1x/day, 7 times a week	2 weeks
Kihara 2004	Far-infrared-ray dry sauna	60°C	15 min	1x/day, 5 times a week	2 weeks
Miyata 2008	Far-infrared-ray dry sauna	60°C	15 min	1x/day, 5 times a week	2 weeks
Kihara 2009	Far-infrared-ray dry sauna	60°C	15 min	5 days after admission, at least 2 times a week after hospital discharge	5 years
Kuwahata 2011	Far-infrared-ray dry sauna	60°C	15 min	1x/day, 5 days a week for 4 weeks	4 weeks
Fujita 2011	Far-infrared-ray dry sauna	60°C	15 min	1x/day	4 weeks
Tei 2016	Far-infrared-ray dry sauna	60°C	15 min	1x/day, 5 times a week for 2 weeks	2 weeks
Ichiki 2017	Far-infrared-ray dry sauna	60°C	15 min	1x/day, 5 times a week for 2 weeks	2 weeks
Basford 2009	Far-infrared-ray dry sauna	60°C	15–20 min	3 times a week for 4 weeks	4 and 4 weeks

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Table 4. Summary of findings table. HF, Heart failure; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEDD, left ventricular end diastolic diameter; EF, left-ventricular ejection fraction; LAD, left atrial diameter; BNP, b-type natriuretic peptide; CTR, cardiothoracic ratio.

Summary of findings
Population: HF patients

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Intervention: sauna bath						
Control: No sauna bath						
	Mean difference	**CI95%**	**No. of participants (sauna/control)**	**Heterogeneity**	**Quality of evidence (Modified GRADE) supporting the intervention**	**Comments**
Outcomes						
SBP	-2.58	-5.86 to 0.70	275/216	I2 = 42%	2 Low	Moderate risk for bias -1, Imprecision -1
DBP	-1.42	-3.89 to 1.05	199/143	I2 = 27%	2 Low	Moderate risk for bias -1, Imprecision -1
LVEDD	-1.07	-2.20 to 0.07	228/169	I2= 58%	1 Insufficient	Moderate risk for bias -1, Heterogeneity -1, Imprecision -1
EF	1.45	0.55 to 2.35	275/226	I2 = 0%	3 Moderate	Moderate risk for bias -1
LAD	-0.32	-1.51 to 0.88	228/169	I2 = 25%	2 Low	Moderate risk for bias -1, Imprecision -1
BNP	-124.62	-198.09 to -51.14	160/136	I2 = 37%	3 Moderate	Moderate risk for bias -1
CTR	-1.82	-2.54 to -1.09	275/216	I2 = 31%	3 Moderate	Moderate risk for bias -1

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