Study protocol

Title

Mana**gi**ng **C**ongestion in **H**eart **F**ailure: Pressure- and Volume- based. A mechanistic study in patients with HFpEF **(MAGIC-HF)**

Version: 17.12.2024

INDEX:

1. GENERAL INFORMATION

Principal Investigator:

Tarek Bekfani, Associate Professor, MD, MSc (Oxon.), FESC, FHFA

Co-Investigators:

Alexandar Schmeißer, Prof. Dr. med.

Thomas Rauwolf, PhD

Birgit Aßmus, Prof. Dr. med.

Friedrich Köhler, Prof. Dr. med.

Stefan Störk, Prof. Dr. med.

Rüdiger C. Braun-Dullaeus, Prof. Dr. med. FESC, FACC

William T. Abraham, Prof., MD, FACP, FACC, FAHA, FESC, FRCP

Correspondence:

Department of Internal Medicine, Division of Cardiology, Angiology and Intensive Medical Care, University Hospital Magdeburg, Otto-von-Guericke University, Magdeburg, Germany
Tel.: 0391 67 14469
Fax: 0391 67 13202
E-Mail: tarek.bekfani@med.ovgu.de

Signatures

Name, Principal Investigator Date

Name, Local PI in Giessen University Hospital Date

Name, Local PI in DHZC, Charité, Berlin Date

Name, Local PI at the University Hospital Wuerzburg Date

2. SYNOPSIS

1. Title of study	**Ma**nag**i**ng **C**ongestion in **H**eart **F**ailure: Pressure- and Volume- based. A mechanistic study in patients with HFpEF **(MAGIC-HF)**
2. Hypothesis	We hypothesize that remote monitoring (RM) in patients with heart failure (HF) with preserved (HFpEF) ejection fraction using a smart scale to measure extracellular and total amount of water in different segments of the body in parallel to monitoring pulmonary pressure improves the management of congestion in patients with HF. This leads as a result to an improvement of NT-pro-BNP and renal function.
3. Objective of the study	We plan a mechanistic RM-study in patients with HFpEF, who have the indication for RM using CardioMEMS^{TM}. Data transmitted from CardioMEMS^{TM} and from the smart scale will be monitored on daily basis in order to understand the mechanism of changes taking place during the study duration (6 months) in both pulmonary pressure and in volume represented as extracellular and total amount of water in the upper and lower extremities as well as in the trunk. This should allow us to reach an euvolemic state in patients with HF, which is often an unmet need.
4. Background	In patients with heart failure (HF) the absolute number of hospitalizations and the rates of HF readmissions is still high with a significant financial burden associated. As a result, reducing readmission rates has become a priority in many of the developed countries. Currently 25% of patients with HF are readmitted within one month of discharge. Achieving and maintaining an euvolemic status through managing congestion is a key goal in the management of HF. Thus, close observation of, and rapid response to changes of early physiological indicators are essential in achieving or maintaining euvolemia. Clinical signs and symptoms of cardiac decompensation are preceded by an increase in filling pressures and autonomic adaptation. Furthermore, clinical signs and symptoms are neither sensitive nor specific for detecting congestion. We have shown in a previous study in patients with HF and sleep apnea increased amounts of both extracellular and total amounts of water compared to those with HF but without sleep apnea. The increased amount of water was not associated with clinical cardiac decompensation. We called this clinically pre-congestion. An increased amount of water was associated with worse exercise capacity and with an elevated apnea/hypopnea index. As such, new means and technologies to improve monitoring of such parameters and care delivery are urgently required. Novel technologies of telemedicine or RM such as CardioMEMS^{TM} (Abbott Laboratories, Chicago, IL, USA), which is a small sensor placed in the pulmonary artery to monitor the pulmonary pressure, represent a possible solution to the above-mentioned unmet needs in patients with HF. However, the principle that volume equals pressure has been challenged recently. Based on data from CardioMEMS^{TM} and systems enabling estimation of the intravascular volume such as blood volume analysis (BVA-100, Daxor Corporation, New York, NY, USA), the current approach of HF-Therapy using diuretics to decongest these patients appeared not to be always the best decision. The reason is that some of those patients with elevated pulmonary pressure (CardioMEMS^{TM}) appeared to be euvolemic or hypovolemic. It was postulated that congestion is a result of changes occurring in both volume and pressure. Additionally, severe congestion is supposed to be associated with inflammation, mechanical stress, and endothelial dysfunction. Thus, identifying surrogate biomarkers for all of these processes in addition to monitoring volume and pressure simultaneously

	and continuously for 6 months would help to better understand congestion and its management. This is indeed an important concept and a clinically relevant question to characterize patients in different phenotypes as following: elevated/low pressure with hypervolemic, euvolemic or hypovolemic. Managing congestion in patients with HF might be optimally achieved by both monitoring pulmonary pressure and volume status.
5. Number of patients	20 Patients with HFpEF. Dropout 20%. Total number of patients 25 patients.
6. Number of sites	**Four sites.** - Department of Cardiology and Angiology**,** University Hospital Magdeburg, Germany. - Department of Cardiology and Angiology, University Hospital Giessen, Germany - Department of Cardiology, Deutsches Herzzentrum der Charité, Berlin, Germany - Department of Cardiology, University Hospital Wuerzburg, Germany
7. Length of follow-up	The planned follow-up duration is 6 months Time from first patient in to last patient out 12 months.
8. Data to be collected	All patients will get following tests **at baseline**: **Echocardiography** (left ventricle ejection fraction (LVEF), E/e´, left atrial volume index (LAVI), left atrial strain analysis, left ventricle mass index (LVMI), tricuspid annular plane systolic excursion (TAPSE), right ventricle strain, inferior vena cava IVC), and **blood tests:** N-terminal pro-b-type natriuretic peptide (NT-proBNP), creatinine, glomerular filtrating rate (GFR), soluble suppression of tumorigenicity **(sST2) as a surrogate of intravascular congestion**, carbohydrate antigen 125 **(CA 125)** and bio-adrenomedullin **(bio-ADM)** as surrogates of tissue congestion **(extracellular water)**. Additionally, ALAT, ASAT, complete blood count, and hsCRP will be documented. Evaluation of **extracellular and total amounts of water volume** segmentally (arms, legs, trunk) using the smart scale (Body water scale InBody, South Korea) as well as **pulmonary pressure** (CardioMEMS^{TM}) will be done at the same time. We will gather **daily** data of pulmonary pressure (CardioMEMS^{TM}) and water volume using a smart scale. The evaluation of volume will be based on bioelectric impedance analysis (BIA). **Following blood tests will be monitored at weeks 2, 6, 12 and at the final visit:** NT-proBNP, creatinine and GFR, ALAT, ASAT, hemoglobin, hematocrit, hsCRP, sST2, CA 125, and bio-ADM. Tests and investigations **at the final visit**: Echocardiography (see above), ALAT, ASAT, complete blood count, hsCRP, NT-proBNP, creatinine, GFR, sST2, CA 125, and bio-ADM.
9. Primary and secondary Endpoints	**Explorative analyses of:** • **NT-pro-BNP** • **GFR** • **The percentage of patients who have elevated pulmonary pressure but are hypo- or euvolemic**

3. BACKGROUND AND SIENTIFIC RATIONALE

The absolute number of HF-hospitalizations and the rates of HF readmission is still high with a significant financial burden associated.[1] As a result, reducing readmission rates has become a priority in many of the developed countries.[2,3] Currently 25% of patients with HF are readmitted within one month of discharge and 30% of them within 90 days.[4,5]

Achieving and maintaining an euvolemic status through managing congestion is a key goal in the management of HF. As a response to the reduced cardiac output, the human body attempts to maintain an effective mean arterial pressure through a series of compensatory mechanisms. Over-activation of the sympathetic nervous system and renin–angiotensin–aldosterone system are among the earliest pathophysiological responses[6] along with an increased metabolic rate driven by an active inflammatory process. Over the course of days to weeks, the body starts to retain salt and water. Paired with a decreased vascular compliance due to vasoconstriction, patients at this stage retain fluid, increase cardiac filling pressures, increase interstitial pulmonary fluid, and lastly increase weight.[7] Severe congestion is supposed to be associated with inflammation, mechanical stress, and endothelial dysfunction.[8]

Thus, close observation of, and rapid response to changes to early patho-physiological indicators are essential in achieving and maintaining euvolemia. However, congestion as a clinical marker of cardiac decompensation, which is defined clinically as peripheral edema (ankle, sacral, scrotal), jugular vein distention, pleural effusion, or ascites,[9] is preceded by an increase in filling pressures and autonomic adaptation. Furthermore, clinical signs and symptoms are neither sensitive nor specific for detecting congestion. Additionally, we have shown in a previous study in patients with HF and sleep apnea increased amounts of both extracellular and total amounts of water compared to those with HF but without sleep apnea. This increased amount of water was not associated with overt clinical cardiac decompensation. We called this clinically pre-congestion.[10] The amount of water was associated with worse exercise capacity and with higher values of apnea/hypopnea index.

As such, new means and technologies to improve monitoring of such parameters and care delivery are urgently needed. Novel technologies of telemedicine or remote monitoring (RM) such as CardioMEMS™ (Abbott Laboratories, Chicago, IL, USA)

represents a good solution to the above-mentioned unmet needs in patients with HF.[11,12] Pulmonary artery-pressure-guided management of patients with HF proved to reduce morbidity and mortality in this group of patients. However, the principle that volume equals pressure was challenged recently. Based on data from CardioMEMS™ and systems enabling estimation of the intravascular volume such as blood volume analysis (BVA-100, Daxor Corporation, New York, NY, USA), the current approach of HF-therapy using diuretics to decongest these patients appeared not to be always the best clinical decision. The reason is that some of those patients with elevated pulmonary pressure (CardioMEMS™) appeared to be euvolemic or hypovolemic.[13] It was postulated that congestion is a result of changes occurring in both volume and pressure.

Currently, there is no study that evaluated continuously and simultaneously both volume and pressure in patients with HF. This is indeed an important approach and clinically relevant question since this might lead to an adjustment of our practice by characterizing or phenotyping congested patients into elevated/low pressure with hypervolemic, euvolemic or hypovolemic. Managing congestion in patients with HF might be optimally achieved by both monitoring pulmonary pressure and volume status. Additionally, using surrogate biomarkers could be very helpful in better understanding congestion and its management.

4. OBJECTIVE AND HYPOTHESIS

4.1 OBJECTIVE OF THE STUDY

We plan a mechanistic RM-study in patients with HF with preserved ejection fraction (HFpEF), who have the indication for RM using CardioMEMS™. Data transmitted from CardioMEMS™ and from the smart scale (BWA) will be monitored on daily basis in order to understand the mechanism of changes taking place during the study duration (6 months) in both pulmonary pressure and in volume represented as extracellular and total amount of water in upper and lower extremities as well as in the trunk. This should allow us to reach an euvolemic state in patients with HF, which is often an unmet need. This is especially true in patients with HFpEF.

4.2 HYPOTHESIS

Pulmonary artery pressure-guided management of HF patients through CardioMEMS^{TM} is a well-established and evidenced-based method to reduce mortality and hospitalization rate for HF. We hypothesize that expanding RM by using a smart scale (BWA) to measure extracellular and total amount of water in different body compartments would improve the management of congestion in patients with HF. Furthermore, the data of our study will lead to a new paradigm characterizing different phenotypes of patients with HFpEF with different pressure-volume constellations. By adjusting the HF-management accordingly, an improvement of NT-pro-BNP and renal function is expected to occur.

5. PRIMARY AND SECONDARY ENDPOINTS

In this pilot mechanistic study, we are focusing on understanding the pressure-volume relationship. Thus, our endpoints will be an explorative analysis of:

- NT-pro-BNP
- GFR
- The percentage of patients who have elevated pulmonary pressure but are hypo- or euvolemic.

NT-pro-BNP will be corrected for BMI by reducing 4% per BMI unit over 25 kg/m^2. This formular was applied similarly in the Guide-HF-trial. [14,15]

6. DURATION OF THE STUDY AND THE PLANNED TESTS

The planed follow-up duration is 6 months. Time from first patient in to last patient out will be 12 months.

All patients will get following tests at baseline: Echocardiography (left ventricle ejection fraction (LVEF), E/e´, left atrial volume index (LAVI), left atrial strain analysis, left ventricle mass index (LVMI), tricuspid annular plane systolic excursion (TAPSE), right ventricle strain, inferior vena cava IVC), and blood tests: N-terminal pro-b-type natriuretic peptide (NT-proBNP), creatinine, glomerular filtrating rate (GFR), soluble suppression of tumorigenicity (sST2) as a surrogate of intravascular congestion,

carbohydrate antigen 125 (CA 125) and bio-adrenomedullin (bio-ADM) as surrogates of tissue congestion (extracellular water). Additionally, ALAT, ASAT, complete blood count, and hsCRP will be documented. Evaluation of extracellular and total amounts of water volume segmentally (arms, legs, trunk) using the smart scale (BWA) as well as pulmonary pressure (CardioMEMS^{TM}) will be done daily at the same time.

Following blood tests will be monitored **at days 14, 42, 90** and at the final visit: NT-proBNP, creatinine and GFR, hemoglobin, hematocrit, hsCRP, sST2, CA 125, and bio-ADM.
Blood draw will be 20 ml Blood (Serum and EDTA) in each visit.

Tests and investigations at the final visit: Echocardiography (see above), ALAT, ASAT, complete blood count, hsCRP, NT-proBNP, creatinine, GFR, sST2, CA 125, and bio-ADM.

Bioelectrical-Impedance Analysis (BIA): It is a non-invasive measurement of the body composition, i.e. muscle, fat, water. Measurements will be performed in standing positions using (Body water scale InBody, South Korea), which is capable to measure body amounts of water in different compartment non-invasively, reliably, and objectively based on bioelectric impedance (BIA)-technology. Patients who have implanted cardiac devices will be excluded.[16]

7. RESEARCH DESIGN & METHODOLOGY

7.1 STUDY DESIGN

MAGIC-HF is a streamlined, prospective, mechanistic, non-randomized, study. This study will investigate the value of adding volume-based RM to the well-established pulmonary artery pressure monitoring in patients with HFpEF in understanding the volume-pressure relationship. The study will take place in the department of cardiology, University Hospital Magdeburg.

7.2 STUDY POPULATION

Inclusion criteria:

1) 18 years of age or older.
2) Patients with HFpEF hospitalized for acute decompensated heart failure and require treatment with intravenous (IV) diuretics.
3) signed informed consent.

Exclusion criteria:

1) Patients admitted with cardiogenic shock and/or those who required inotropic or vasopressor support.
2) had a history of cardiac transplantation or ventricular assist device (VAD) implantation.
3) had any implanted cardiac device (pacemaker, ICD, CRT-D.
4) had chronic kidney disease with creatinine clearance < 20 ml/min.
5) had recent acute MI or CABG within 3 months.

Timetable of the study: All participants will undergo a standardized series of assessments as shown in table 1.

Table 1: Timetable of the study

	Day 0	daily	Day 14	Day 42	Day 90	Day 180
Informed consent	x					
Echocardiography	x					x
Body composition-Water assessment	x	x	x	x	x	x
CardioMEMS™-Measurement	x	x	x	x	x	x
Blood tests	x		x	x	x	x

8. PROJECT TIMELINE & FUTURE PLANS

We will be able to begin our study in April 2024. We have previous experience with an established HF population. We expect to reach full recruitment by the end of 2024. Data will be analyzed immediately with focus on presenting initial results in the annual meeting of the European society of Cardiology 2025. We expect to have a full analysis for manuscript preparations by June 2025.

9. PARTICIPATING DEPARTMENT

Department: Department of Cardiology and Angiology, University Hospital Magdeburg
Telefon-Nummer: 0391 67 14469
E-Mail: tarek.bekfani@med.ovgu.de

10. INFORMATION & INFORMED CONSENT

Subjects will sign an informed consent before any investigation of the designed study will be conducted.

11. SAMPLE SIZE AND STATISTICS

There is not enough prior data to calculate the sample size. Our aim primarily is to describe the relationship between pressure-volume as part of the management of HF-management. We suppose that in this pilot study 20 patients should be sufficient to understand this relationship and the mechanism beyond it. With expected 20% drop-out rate, we intend to recruit 25 patients.

All data and statistics will be reported as mean ± standard deviation (n ± SD) for continuous normally distributed data or as median and interquartile range [25–75%] for variables that were not normally distributed, respectively. Categorical data will be summarized by percentages. Kaplan-Meier analyses with a log-rank test will be used for presenting time-to-event data. Daily measurements of CardioMEMS™ and BWA will

be depicted over the study time. A comparison between events represented by increased pulmonary pressure and increased volume higher than the defined cut-off for each patient respectively will be performed. The Statistical Package for Social Sciences software (SPSS 28, IBM, Armonk, USA) will be used for statistical analysis. The chi-squared test will be used to look for trend for categorical variables and Kruskal Wallis test will be applied for not normally distributed data, respectively. Analysis of variance (ANOVA), Pearson's or Spearman simple regression will be used as appropriate. A two-tailed p-value <0.05 indicates statistical significance.

12. STATISTICAL ANALYSIS PLAN (SAP)

Here is a summary of SAP:

Exploratory outcomes: NT-pro-BNP, GFR, and the percentage of patients who have elevated pulmonary pressure but are hypo- or euvolemic.

General considerations: The intention- to-treat will be applied.

Data presentation: Kaplan Meier curves will be constructed for time-to-event analyses. Log rank test will be used to compare between groups.

Missing data handling: To minimize missing data, all measurements will be taken to collect all essential data. Still missing data will be dealt with suing a multiple imputation model.

13. SAFEGUARD FOR THE PROTECTION OF PATIENT SAFETY AND WELFARE

Participation is entirely voluntary and will in no way effect their care. There is no direct benefit to the patients except a strong contribution to science.

Blood samples will be taken during the outpatient visits at low risk. Adverse events will be reviewed on a biweekly basis by a cardiologist otherwise not affiliated with this proposal. Serious adverse events will be reported to the Institutional Review Board within 24 hours. All patient information will be kept absolutely confidential.

13.1. ETHICAL ASPECTS

Prior to the start of the study, all required approvals from the local ethic committee will be obtained. The Study fulfills all principles of the Declaration of Helsinki and good clinical practice and will adhere to the protocol. The study will be registered at clinicaltrials.gov.

14. FUNDING

An application for a research grant from Abbott has been submitted.

15. FINAL REPORT & PUBLIATIONS

Data will be analyzed immediately with focus on presenting initial results in the annual meeting of the German Society of Cardiology and European Society of Cardiology. We expect to have a full analysis for manuscript preparations by June 2025. A copy of the final report / publications will be submitted to the ethic commission.

16. INSURANCE

In this clinical study, all study participants are covered by the liability insurance of the University Hospital Magdeburg A.ö.R.

17. DATA PROTECTION

During the study, medical findings and personal information will be collected from you and written down in your personal study file and/or stored electronically in our department for Cardiology and Angiology. In accordance with the currently valid data protection regulations (EU Data Protection Regulation/DS-GVO, State Data Protection of Saxony-Anhalt), the study data will additionally be stored in pseudonymized form, evaluated and, if necessary, passed on to other authorized persons. "Pseudonymized" means that no details of clear names or complete birth data are used, but only a

number and/or letter code and your personal data are only known to authorized persons in the clinic. The data are secured against unauthorized access from outside. All data collected during the clinical study shall be published in anonymous form.
Records and documents relevant to the study (e.g. informed consent forms) will be kept in the University Hospital Magdeburg, Department of Cardiology and Angiology for at least 15 years.
Patient records and other original data must be kept for the longest possible period provided by Magdeburg University Hospital A.ö.R. (10 years) and secured against unauthorized access.

18. REFERENCES

1. Epstein AM, Jha AK, Orav EJ. The relationship between hospital admission rates and rehospitalizations. *N Engl J Med*. 2011;365:2287-2295. doi: 10.1056/NEJMsa1101942
2. Dickinson MG, Allen LA, Albert NA, DiSalvo T, Ewald GA, Vest AR, Whellan DJ, Zile MR, Givertz MM. Remote Monitoring of Patients With Heart Failure: A White Paper From the Heart Failure Society of America Scientific Statements Committee. *J Card Fail*. 2018;24:682-694. doi: 10.1016/j.cardfail.2018.08.011
3. Brahmbhatt DH, Cowie MR. Remote Management of Heart Failure: An Overview of Telemonitoring Technologies. *Card Fail Rev*. 2019;5:86-92. doi: 10.15420/cfr.2019.5.3
4. van Oeffelen AA, Agyemang C, Stronks K, Bots ML, Vaartjes I. Prognosis after a first hospitalisation for acute myocardial infarction and congestive heart failure by country of birth. *Heart*. 2014;100:1436-1443. doi: 10.1136/heartjnl-2013-305444
5. Ryan AM, Nallamothu BK, Dimick JB. Medicare's public reporting initiative on hospital quality had modest or no impact on mortality from three key conditions. *Health Aff (Millwood)*. 2012;31:585-592. doi: 10.1377/hlthaff.2011.0719
6. Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. *N Engl J Med*. 1999;341:577-585. doi: 10.1056/NEJM199908193410806
7. Kaye DM, Lefkovits J, Jennings GL, Bergin P, Broughton A, Esler MD. Adverse consequences of high sympathetic nervous activity in the failing human heart. *J Am Coll Cardiol*. 1995;26:1257-1263. doi: 10.1016/0735-1097(95)00332-0
8. Pandhi P, Ter Maaten JM, Anker SD, Ng LL, Metra M, Samani NJ, Lang CC, Dickstein K, de Boer RA, van Veldhuisen DJ, et al. Pathophysiologic Processes and Novel Biomarkers Associated With Congestion in Heart Failure. *JACC Heart Fail*. 2022;10:623-632. doi: 10.1016/j.jchf.2022.05.013
9. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the

Heart Failure Association (HFA) of the ESC. *European Heart Journal*. 2021;42:3599-3726. doi: 10.1093/eurheartj/ehab368

10. Bekfani T, Schobel C, Pietrock C, Valentova M, Ebner N, Dohner W, Schulze PC, Anker SD, von Haehling S. Heart failure and sleep-disordered breathing: susceptibility to reduced muscle strength and preclinical congestion (SICA-HF cohort). *ESC Heart Fail*. 2020;7:2063-2070. doi: 10.1002/ehf2.12798
11. Brugts JJ, Radhoe SP, Clephas PRD, Aydin D, van Gent MWF, Szymanski MK, Rienstra M, van den Heuvel MH, da Fonseca CA, Linssen GCM, et al. Remote haemodynamic monitoring of pulmonary artery pressures in patients with chronic heart failure (MONITOR-HF): a randomised clinical trial. *Lancet*. 2023;401:2113-2123. doi: 10.1016/s0140-6736(23)00923-6
12. Givertz MM, Stevenson LW, Costanzo MR, Bourge RC, Bauman JG, Ginn G, Abraham WT. Pulmonary Artery Pressure-Guided Management of Patients With Heart Failure and Reduced Ejection Fraction. *J Am Coll Cardiol*. 2017;70:1875-1886. doi: 10.1016/j.jacc.2017.08.010
13. Yaranov DM, Jefferies JL, Silver MA, Burkhoff D, Rao VN, Fudim M. Discordance of Pressure and Volume: Potential Implications for Pressure-Guided Remote Monitoring in Heart Failure. *J Card Fail*. 2022;28:870-872. doi: 10.1016/j.cardfail.2022.02.003
14. Lindenfeld J, Zile MR, Desai AS, Bhatt K, Ducharme A, Horstmanshof D, Krim SR, Maisel A, Mehra MR, Paul S, et al. Haemodynamic-guided management of heart failure (GUIDE-HF): a randomised controlled trial. *The Lancet*. 2021;398:991-1001. doi: https://doi.org/10.1016/S0140-6736(21)01754-2
15. Frankenstein L, Remppis A, Nelles M, Schaelling B, Schellberg D, Katus H, Zugck C. Relation of N-terminal pro-brain natriuretic peptide levels and their prognostic power in chronic stable heart failure to obesity status. *Eur Heart J*. 2008;29:2634-2640. doi: 10.1093/eurheartj/ehn388
16. Liu MH, Wang CH, Huang YY, Tung TH, Lee CM, Yang NI, Wang JS, Kuo LT, Cherng WJ. Edema index-guided disease management improves 6-month outcomes of patients with acute heart failure. *Int Heart J*. 2012;53:11-17. doi: 10.1536/ihj.53.11