D-A-CH DREILÄNDER TREFFEN HERZ-INSUFFIZIENZ

28.–30. September 2023

Programm

D-A-CH Dreiländertreffen Herzinsuffizienz

Göttingen, Deutschland

Liebe Kolleginnen und Kollegen, liebe Freunde,

wir freuen uns, Sie in diesem Jahr zum traditionellen Dreiländertreffen in Göttingen begrüßen zu dürfen. Göttingen ist etwas Besonderes, da sich das Treffen bisher selten so weit in den Norden verirrt hat. Trotzdem ist es uns gelungen, eine ausgewiesene Faculty aus Deutschland, Österreich und der Schweiz nach Südniedersachsen einzuladen. Wir hoffen auf informative Vorträge, angeregte Diskussionen und natürlich ein spannendes Rahmenprogramm, sodass wir genügend Zeit haben, uns zu verschiedenen Aspekten der Herzinsuffizienz auszutauschen

Das Thema Herzinsuffizienz wird immer relevanter, da wir in den letzten Jahren einen regelrechten Boom an neuen Erkenntnissen und Therapiemöglichkeiten erlebt haben, die uns als Ärztinnen und Ärzten breites Wissen abverlangen und für die Patientinnen und Patienten neue Möglichkeiten aufzeigen.

Das eigentliche Dreiländertreffen beginnt am Donnerstag zur Mittagszeit. Trotzdem geht es schon früher los mit dem Treffen der Jungen Herzmedizin, einem Treffen zum Thema Heart and Brain, das die interdisziplinäre Vernetzung betont, sowie einem parallelen Treffen für das nichtärztliche Assistenz- und Pflegepersonal.

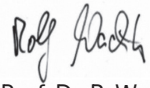
Dankbar sind wir unseren Sponsoren, ohne die ein solches Treffen nicht realisierbar wäre. Daneben natürlich der Öffentlichkeitsarbeit des Herzzentrums und auch der Agentur MedEd GS, die sich um die Logistik kümmert.

In diesem Sinne: Herzlich willkommen

Ihre

Prof. Dr. Dr. S. von Haehling
(Göttingen)

PD Dr. K. Hellenkamp
(Göttingen)



Prof. Dr. R. Wachter
(Leipzig)

Inhaltsverzeichnis

D-A-CH Kardiologische Gesellschaften

Univ.-Prof. Dr. Dr. Stephan von Haehling, Göttingen, Deutschland
Univ. -Prof. Dr. Stefan Frantz, Würzburg, Deutschland
Univ.-Prof. Dr. Philip Raake, Heidelberg, Deutschland

Assoz. Prof. DDr. Peter Rainer, Graz, Österreich
Prim. Dr. Anna Rab, Schwarzach St. Veit, Österreich
Priv. Doz. Dr. Christopher Adlbrecht, Wien, Österreich

Prof. Dr. Andreas Flammer, Zürich, Schweiz
Dr. Matthias Paul, Luzern, Schweiz
Prof. Dr. Micha Maeder, St. Gallen, Schweiz

Lokales Organisationskomitee
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Priv. Doz. Dr. Kristian Hellenkamp, Göttingen, Deutschland
Univ.-Prof. Dr. Rolf Wachter, Leipzig, Deutschland
Anja Eckermann, Göttingen, Deutschland

Kongressmanagement
Dr. rer. nat. Annika Graß, Göttingen, Deutschland
Anja Janssen, Göttingen, Deutschland
Eva Meyer-Besting, Göttingen, Deutschland

Veranstaltungsort
Georg-August-Universität Göttingen
Tagungs- und Veranstaltungshaus Alte Mensa
Wilhelmsplatz 3
37073 Göttingen

Anmeldung
Foyer der „Alten Mensa“ (Veranstaltungsort)

Öffnungszeiten

Do	28.09.2023 – 08:00 – 18:00 Uhr
Fr	29.09.2023 – 08:00 – 18:15 Uhr
Sa	30.09.2023 – 08:00 – 13:00 Uhr

Industrieausstellung
Im Rahmen der Tagung findet von Donnerstag, 28. September, 12:30 Uhr bis Samstag, 30. September, 10:00 Uhr eine Industrieausstellung statt.

Zertifizierung
Ärztekammer Niedersachsen
20 CME-Punkte

Web
https://dach-herzinsuffizienz.org/

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Hannover, Deutschland

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Diether Kramer
Graz, Österreich

Ingo Kutschka
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Göttingen, Deutschland

Norbert Smetak
Kirchheim, Deutschland

Piotr Sobanski
Schwyz, Schweiz

Christian Sohns
Bochum, Deutschland

Samuel Sossalla
Gießen, Deutschland

Thomas Thum
Hannover, Deutschland

Malte Tiburcy
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Karl Toischer
Göttingen, Deutschland

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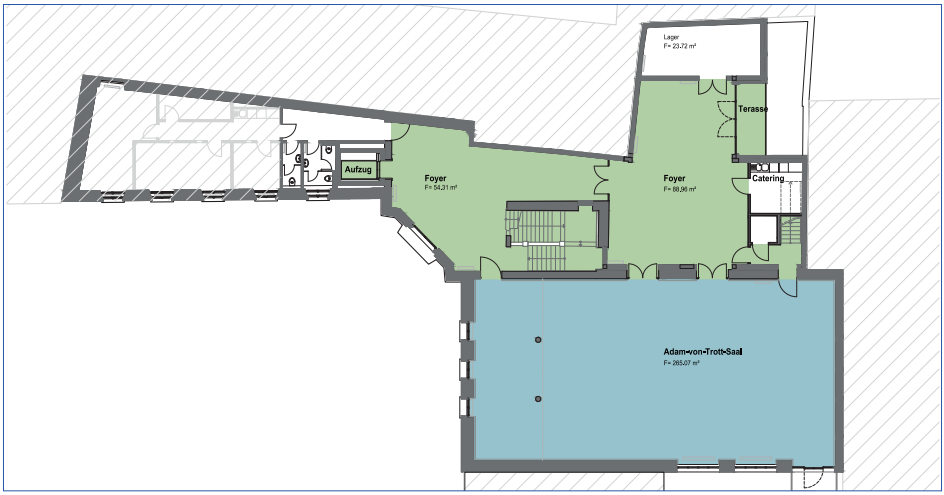
Göttingen, Deutschland

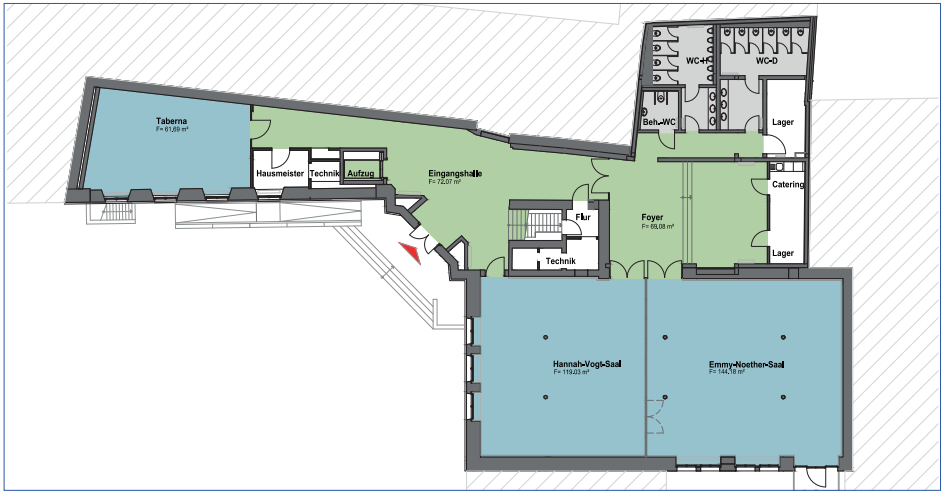
Qian Zhou
Basel, Schweiz

Jana Zschüntzsch
Göttingen, Deutschland

1. OG
Adam-von-Trott-Saal / Hauptvortragssaal



ERDGESCHOSS
Emmy-Noether-Saal & Hannah-Vogt-Saal / Industrieausstellung & Posterausstellung
Taberna / Netzwerk-Café



8:30 – 10:45 Adam-von-Trott-Saal

Junge Herzmedizin

Chair:
Monika Sadlonova (Göttingen)
Djawid Hashemi (Berlin)

8:30 – 8:45
Introduction, Welcome and Vision for the Future
Stephan von Haehling (Göttingen),
Monika Sadlonova (Göttingen),
Djawid Hashemi (Berlin)

8:45 – 9:00
The Role of Inflammation in Heart Failure Post-Myocardial Infarction
Michael Molitor (Mainz)

9:00 – 9:15
The Role of Mitochondria in Atrial Fibrillation
Julius Pronto (Göttingen)

9:15 – 9:30
Ex-VAD – Clinical Trial in Advanced Heart failure
Anna Feuerstein (Berlin)

9:30 – 9:45
Cardiomyopathy Conundrum: Athlete's Heart, ARVC, and Inflammation: A Comparative Analysis
Valentina Rossi (Zürich)

9:45 – 10:00
Biomarkers and Cardiac Remodeling: Connecting the Dots from Cells to Circulation.
Henrike Arfsten (Wien)

10:00 – 10:15
Cardiorenal Syndrome in Heart Failure
Ann-Kathrin Schäfer (Göttingen)

10:15 – 10:25
What do I admire about the other partner sites
All speakers

8:30 – 10:45 Taberna

Assistenzpersonal (Kardiotechnik & Pflege)

Organisation:
Anja Eckermann (Göttingen)

8:30 –09:00
Präsentation eines Manuals zu verhaltensändernden Maßnahmen bei Patient *innen mit Herzinsuffizienz
Oliver Herber (Witten / Herdecke)

9:00 – 10:15
Verschiedene Herzinsuffizienz – Weiterbildungsmöglichkeiten der D-A-CH-Region für nichtärztliches Assistenzpersonal – Voraussetzungen und Befähigungen Weiterbildung...

- **... zur Herzinsuffizienzberatung (A)**
  Elisabeth Kleinheinz (Zams)
- **... zur „Spezialisierten Herzinsuffizienz Assistenz" (D)**
  Anja Eckermann (Göttingen)
- **... zur Heart Failure Nurse am DZHI Würzburg (D)**
  Gabriele Hartner (Würzburg)
- **... zum/zur "Pflegeexperten / in Herzinsuffizienz" (D)**
  Jens Keinhorst (Essen)
- **... Herzinsuffizienzberater* innen (CH)**
  Thorsten Arp (Mammern)

Diskussionsrunde
Stefan Störk (Würzburg)

10:15 – 10:45
Psychokardiologie – die Rolle der Pflegenden
Christoph Herrmann Lingen (Göttingen)

10:45 – 11:00 Foyer 1.OG

Pause

11:00 – 12:30 Adam-von-Trott-Saal

Heart & Brain: Wohin strebt die Forschung?

Chair:
Qian Zhou (Basel)
Gerd Hasenfuß (Göttingen)

11:00 – 11:12
Die Sicht der Grundlagenwissenschaftlerin
Elisabeth Zeisberg (Göttingen)

11:15 – 11:27
Kognitive Funktion – was messen wir eigentlich?
Anna Frey (Würzburg)

11:30 – 11:42
Die Sicht der Neurologin
Jana Zschüntzsch (Göttingen)

11:45 – 11:57
Die Sicht des Kardiologen
Rolf Wachter (Leipzig)

12:00 – 12:12
Interdisziplinäres Forschungskolleg: Herausforderungen & Perspektiven
Dörte Katschinski (Göttingen)

12:15 – 12:27
Was können Tiermodelle zur translationalen Forschung beitragen?
Thorsten Döppner (Giessen)

11:00 – 12:00 Taberna

Drei innovative Wege in der Herzinsuffizienz-Patientenversorgung der D-A-CH Region

- **PVM ein Herzinsuffizienz Versorgungsnetzwerk in Rheinland Pfalz**
  Jan Trinemeier (Rheinland Pfalz)
- **herzMobil in Österreich**
  Elisabeth Kleinheinz (Innsbruck)
- **Zwischen Klinik und zu Hause – mit dem E-Bike zu den Patienten*innen**
- Valerie Epking-Veltman (Basel)

12:00 – 12:30 Taberna

Genderspezifische Unterschiede bei Herzinsuffizienz

Anja Sandek (Göttingen)

12:30 – 13:00 Foyer EG

Pause

13:00 – 13:15
Kongresseröfnung

13:15 – 14:45 Adam-von-Trott-Saal

Pipeline zur Therapie der Herzinsuffizienz

Vorsitz:
Peter Rainer (Graz)
Thomas Thum (Hannover)

13:15 – 13:25
Pirfenidon
Susanne Lutz (Göttingen)

13:30 – 13:40
Ponsegromab: GDF-15 Inhibition
Tibor Kempf (Hannover)

13:45 – 13:55
Relaxin
Thomas Dschietzig (Bensheim)

14:00 – 14:10
BioVAT
Malte Tiburcy (Göttingen)

14:15 – 14:25
Mirabegron
Micha Maeder (St. Gallen)

14:30 – 14:40
Sumanirole
Tobias Pfeffer (Hannover)

14:45 – 15:15 Foyer 1.OG

Pause

15:15 – 16:45 Adam-von-Trott-Saal

Herzinsuffizienz mit erhaltener Ejektionsfraktion (HFpEF)

Vorsitz:
Markus Wallner (Graz)
Norbert Frey (Heidelberg)

15:15 – 15:30
HFpEF: Eine diagnostische Herausforderung
Frank Edelmann (Berlin)

15:35 – 15:50
Fallstricke bei klinischen Studien – Warum funktionieren SGLT2-Inhibitoren und alles andere nicht?
Diana Bondermann (Wien)

15:55 – 16:10
Eine heterogenes Patientenkollektiv – Komorbiditäten und individualisiertes Management bei HFpEF
Kristian Hellenkamp (Göttingen)

16:15 – 16:30
Autonome Funktion bei HFpEF
Philipp Wild (Mainz)

16:30 – 16:45
Panel-Diskussion

16:45 – 17:00 Foyer 1.OG

Pause

17:00 – 18:00 Adam-von-Trott-Saal

Satellitensymposium 1 (Sponsor: Pfizer)

Herzinsuffizienz und keine Besserung – Was kann ich tun?

Vorsitz :
Fabian Knebel (Berlin)
Stephan von Haehling (Göttingen)

Differentialdiagnose bei Herzinsuffizienz mit erhaltener Pumpfunktion: Von Zebras und Chamäleons
Birgit Aßmus (Gießen)

Von der Theorie zur Praxis: Aus dem Alltag eines Amyloidose-Zentrums
Anja Hänselmann (Hannover)

Der ATTR-Patient - Herausforderungen und Chancen in der nuklearmedizinischen Bildgebung
Christoph Rischpler (Stuttgart)

Ab 19:00

Gemeinsames Abendessen im Deutschen Theater (Theaterplatz)

Voranmeldung erforderlich

8:30 – 9:30 Adam-von-Trott-Saal

Elektrophysiologische Aspekte bei Herzinsuffizienz

Vorsitz:
Felix Mahfoud (Homburg)
Samuel Sosalla (Gießen/Bad Nauheim)

8:30 – 8:40
Herzinsuffizienz und nicht permanentes Vorhofflimmern – PV-Ablation für alle?
Leonard Bergau (Göttingen)

8:45 – 8:55
Herzinsuffizienz und permanentes Vorhofflimmern – Pace and Ablate für alle?
Christian Sohns (Bochum)

9:00 – 9:10
CRT, CSP & CCM bei Patienten mit Herzinsuffizienz
Stephan Winnik (Zürich)

9:15 – 9:25
Primärprophylaxe des plötzlichen Herztodes bei Herzinsuffizienz & Kardiomyopathien: Was gibt es Neues?
Marianne Gwechenberger (Wien)

9:30 – 9:55 Foyer 1.OG

Pause

9:55 – 10:55 Adam-von-Trott-Saal

Akute Herzinsuffizienz

Vorsitz:
Kristian Hellenkamp (Göttingen)
Georhias Kollias (Linz)

9:55 – 10:05
Kardiogener Schock – State of the art
Karl Toischer (Göttingen)

10:10 – 10:20
Rhythmologisches Management bei VT-Sturm
Ardan Saguner (Zürich)

10:25 – 10:35
Akute Rechtsherzinsuffizienz und Pulmonale Hypertonie
Stephan Rosenkranz (Köln)

10:40 – 10:50
Medikamentöse Therapie: Alles nur Diurese?
Christian Schulze (Jena)

11:00 – 12:00 Adam-von-Trott-Saal

Satellitensymposium 2 (Sponsor: Boehringer Ingelheim)

Paradigmenwechsel in der Behandlung der Herzinsuffizienz

Vorsitz:
Stefan D. Anker (Berlin)
Michael Böhm (Homburg)

11:00 – 11:20
Neue Therapiestrategien für Patienten mit Herzinsuffizienz
Rolf Wachter (Leipzig)

11:20 – 11:40
EMPULSE Studie: Wirkung von Empagliflozin bei akuter Herzinsuffizienz
Christiane Angermann (Würzburg)

11:40 – 12:00
Herzinsuffizienz und Niere: Was gilt es zu beachten?
Roland Schmieder (Erlangen)

12:00 – 13:00

Mittagessen (Flying Buffet) Foyer EG
Moderierte Posterausstellung Hanna-Vogt-Saal

Poster-Session I

Leitung:
Tarek Bekfani (Magdeburg)
Natallia Laptseva (Zürich)
Marc-Michael Zaruba (Innsbruck)

I.1 **The use of Electroanatomic Voltage Mapping to diagnose isolated cardiac sarcoidosis**
Martin Grübler

I.2 **LV Dyssynchron at Rest and Under Stress: A Semi-Quantitative Examination o Heart Failure Patients and Controls via Cardiac MRI**
Rebecca Beyer

I.3 **Clinical relevance of the "Risk of Heart Disorders" Score from cloud-based heart health analytics of Holter ECG data (Cardiolyse) for development and progression of heart failure**
Daniel Carstens

I.4 **Right ventricular dysfunction for prediction of long-term recovery in newly diagnosed heart failure with reduced ejection fraction**
Aiste Monika Jakstaite

I.5 **Long-term outcomes following explantation of durable left ventricular assist device**
Aiste Monika Jakstaite

I.6 **Epigenome-wide association study of heart failure uncovers phenotype-specific DNA methylation**
Mykhailo Krolevets

I.7 **The role of MRAS in atherosclerosis and relevant cardiovascular risk factors**
Pashmina Wiqar Shah

I.8 **Iron Deficiency in Heart Failure**
Valentin G. W. Hirsch

I.9 **Angiotensin receptor-neprilysin inhibition improves ventricular-arterial coupling in patients with heart failure and reduced ejection fraction**
Tina Stegmann

I.10 **ESCAPE - eine EU-weite Multicenterstudie zur "Evalation of a patient-centred biopsychoSocial blended Collaborative care Pathway for the treatment of multimorbid Elderly patients**
Christine Zelenak

I.11 **Functional capacity and incidence of sarcopenia in older heart failure patients undergoing inpatient cardiac rehabilitation – an observational cohort study**
Carolin Steinmetz

I.12 **Proteomic profile of chronotropic incompetence reveals differences in the heart failure phenotypes**
Noémie Bélanger

I.13 **Lebensqualität und psychologische Aspekte bei Patienten und ihren Angehörigen nach überlebter ECMO Therapie**
Birgit Jutta Gerecke

I.14 **Die Symptomlast gemessen an der NYHA-Klasse ist ein unabhängiger Faktor für Pruritus bei Patienten mit Herzinsuffizienz**
Samira Soltani

I.15 **Excess RAS activation is attributed to the combination of forward and backward failure in heart failure with reduced ejection fraction**
Henrike Arfsten

Poster-Session II

Leitung:
Danae Parianos (Zürich)
Ruben Evertz (Göttingen)
Martin Hülsmann (Wien)

II.1 **Cardioprotective actions of SGLT2 inhibitors through regulation of EndMT and fibrosis**
Kevin Schmidt

II.2 **Factors Limiting Optimal Medical Therapy only concern a fraction of advanced HFrEF patients and might improve over time**
Annika Weidenhammer

II.3 **Skeletal muscle-selective deletion of iron regulatory proteins increases early mortality and impairs cardiac function after transferse aortic constriction**
Zulaikha Malik

II.4 **Preemptive iron supplementation prevents cardiac iron deficiency and adverse remodelling after myocardial infarction**
Bomee Chung

II.5 **Hypophosphatemia in HFrEF patients after iron supplementation - ferrich carboxymaltose vs. Ferric derisoaltose**
Noel Gilian Panagiotides

II.6 **Iron Deficiency is Associated with Higher Fibroblast Growth Factor 23 Levels in Patients with Chronic Heart Failure: Results from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF)**
Ryosuke Sato

II.7 **Novel biomarkers as possible prognostic tools in the determination of muscle wasting in HF patients**
Tania Garfias-Veitl

II.8 **Body mass-related epigenetic and transcriptional reprogramming in heart failure phenotypes**
Elif Yapici

II.9 **Pericyte and smooth muscle specific knock-out of CXCL12 and its influence on cardiac function after myocardial ischemia in mice**
Simon Staggl

II.10 **Refinement of cardiac repair after myocardial infarction in mice: Impact of HIF-1a upregulation de to prolyl-hydroxylase inhibition with roxadustat**
Simon Staggl

II.11 **Molecular mechanisms of cardiac natriuretic peptide effect on adrenal aldosterone secretion**
Sanika Mohagaonkar

II.12 **Cardiac fibrosis fingerprints and pre-clinical development of therapeutic approaches**
Maria Jordan

II.13 **Assessment of cardiotoxicity via organomimetic 2D and 3D models**
Mandy Otto

II.14 **MicroRNA-22 as a potential diagnostic tool in patients with heart failure and sarcopenia: Results from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF) and the Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies (SPRINTT)**
Mirela Vatic

II.15 **Sex-related differences in heart failure pharmacological treatment: Results from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF)**
Mirela Vatic

13:00 – 13:30 Adam-von-Trott-Saal

D-A-CH Lecture

Vorsitz:
Stephan von Haehling (Göttingen)
Michael Böhm (Homburg)

13:00 – 13:30
D-A-CH Lecture
Gerd Hasenfuß (Göttingen)

13:30 – 14:30 Adam-von-Trott-Saal

Erweiterte Diagnostik bei Herzinsuffizienz

Vorsitz:
Miroslava Valentová (Göttingen)
Philipp Raake (Augsburg)

13:30 – 13:40
Kardiales MRT zur ätiologischen Abklärung
Andreas Schuster (Göttingen)

13:45 – 13:55
Einsatz von KI in der kardiologischen Prävention
Diether Kramer (Graz)

14:00 – 14:10
Die Sicht des niedergelassenen Kardiologen
Norbert Smetak (Kirchheim)

14:15 – 14:25
Basics Spiroergometrie
David Niederseer (Zürich)

14:30 – 14:45 Foyer EG

Pause

14:45 – 15:45 Adam-von-Trott-Saal

Satellitensymposium 3 (Sponsor: Novartis)

Herzinsuffizienzmanagement 2023 – Wie sollten wir es machen?

Vorsitz:
Stephan von Haehling (Göttingen)
Gerd Hasenfuß (Göttingen)

14:45 -15:15
Verbessert die Versorgungsstruktur die Behandlungsqualität der Herzinsuffizienz?
Birgit Aßmus (Gießen)

15:15 – 15:45
Komplexes Krankheitsgeschehen bei HFrEF – Behandeln wir medikamentös adäquat?
Michael Böhm (Homburg)

14:45 – 15:45 Taberna

Pflege: Netzwerk-Café - Come together

Zeit zum allgemeinen Austausch mit Teilnehmenden und Referierenden

15:45 – 17:00 Adam-von-Trott-Saal

Herzinsuffizienz in besonderen Situationen

Vorsitz:
Martin Hülsmann (Wien)
Stefan D. Anker (Berlin)

15:45 – 16:00
... in und um die Schwangerschaft
Johann Bauersachs (Hannover)

16:05 – 16:20
... bei kardialer Hypertrophie: Diagnostisches Vorgehen
Nicolas Verheyen (Graz)

16:25 – 16:40
... auf Reisen
Stephan von Haehling (Göttingen)

16:45 – 17:00
... wenn die Symptome persistieren, oder das Ende der Fahnenstange naht. Palliative Care bei Herzinsuffizienz
Piotr Sobanski (Schwyz)

17:00 – 17:15

Pause

17:15 – 18:15 Adam-von-Trott-Saal

Satellitensymposium 4 (Sponsor: AstraZeneca)

Wie setzen wir die HI-Leitlinie zur optimalen Therapie im Netzwerk um?

Vorsitz:
Stephan von Haehling (Göttingen)
Karin Rybak (Dessau)

17:15 – 17:35
Diagnostik der Herzinsuffizienz
Caroline Morbach (Würzburg)

17:35 – 17:55
Leitliniengerechte Umsetzung der Herzinsuffizienztherapie
Tibor Kempf (Hannover)

17:55 – 18:15
Paneldiskussion: "Wie setzen wir die HI-Leitlinie zur optimalen Therapie im Netzwerk um“?

18:30

Stadtführung „Rund ums Gänseliesel“ mit Aula und Karzer

Treffpunkt vor der Alten Mensa (Anmeldung erforderlich)

8:30 – 9:45 Adam-von-Trott-Saal

Interventionelle und operative Therapieoptionen bei Herzinsuffizienz

Vorsitz:
Stefan Frantz (Würzburg)
Ingo Kutschka (Göttingen)

8:30 – 8:42
Wer profitiert von einer Therapie seiner Mitral- und Trikuspidalklappeninsuffizienz und wie sollte man behandeln?
Johannes Gollmer (Graz)

8:45 – 8:57
Interatriales Shunting: Design, Strömungsdynamik und klinische Erkenntnisse
Stefan D. Anker (Berlin)

9:00 – 9:12
Herzinsuffizienz und TAVI-Implantation: Wo stehen wir?
Tim Seidler (Göttingen)

9:15 – 9:27
LVAD und HTX: Die Sicht des Kardiologen
Andreas Flammer (Zürich)

9:30 – 9:42
LVAD und HTX: Die Sicht der Herzchirurgin
Julia Dumfarth (Innsbruck)

9:45- 10:15 Foyer EG

Pause

10:15 – 11:50 Adam-von-Trott-Saal

Herzinsuffizienz bei speziellen Herzerkrankungen

Vorsitz
Matthias Paul (Luzern)
Christiane Angermann (Würzburg)

10:15 – 10:30
Der onkologische Patient: Rolle des „Cardiac Wasting“
Markus Anker (Berlin)

10:35 – 10:50
Kardiale Sarkoidose
Michele Martinelli (Bern)

10:55 – 11:10
Myokarditis
Gerhard Pölzl (Innsbruck)

11:15 – 11:30
Takotsubo
Otmar Pfister (Basel)

11:35 – 11:50
Gemeinsame Diskussion

12:00 – 13:00 Adam-von-Trott-Saal

Satellitensymposium 5 (Sponsor: Pharmacosmos)

Herzinsuffizienz und Eisenmangel 2023: Was wissen wir – wo stehen wir – was kommt?

Vorsitz:
Stephan von Haehling (Göttingen)

12:00 – 12:20
Die Wissenschaft dahinter
Tibor Kempf (Hannover)

12:20 – 12:40
Die Studienlage
Christian Schulze (Jena)

12:40 – 13:00
Die Therapie nach den neuen ESC-Leitlinien 2023
Sabine Genth-Zotz (Mainz)

13:00 – 13:30 Adam-von-Trott-Saal

Kongressabschluss
Preisverleihung
Abschließende Worte

13:30 – 14:00 Foyer 1.OG

Mittagessen (Lunch-Boxen)

14:00 – 15:00

Tour durch Herzzentrum und Heart and Brain-Center

(Anmeldung erforderlich)

I.1
The use of Electroanatomic Voltage Mapping to diagnose isolated cardiac sarcoidosis

M.R. Grübler[1], M. Pfeffer[1,2], A. Haiden[1], M. Tscharre[1], L. Fiedler[1,2], FX Roithinger[1,2]
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Introduction: Diagnosing isolated cardiac sarcoidosis is a major diagnostic challenge and relies on non-invasive imaging findings and endomyocardial biopsies (EMB). Unfortunately, EMB is limited by a significant sampling error leading to diagnostic uncertainty and inadequate treatment. Electroanatomic voltage mapping (EAM) guided EMB is a novel concept to improve the diagnostic yield and lower sampling error. By targeting low voltage areas guided biopsies are more likely to represent areas of the diseased myocardial segments. We report a case series of suspected cardiac sarcoidosis and the use of EAM guided EMB.
Methods: We included three patients scheduled for EMB case series. All procedures were guided by endocavitary EAM acquired with the Advisor HD Grid mapping-catheter (Abbott, USA). EAM included a 3D reconstruction of the left (LV) and/or right ventricle (RV) as well as intracardiac ECG recording. The electroanatomic map was used to localize areas of low voltage representing diseased myocardium. Endomyocardial samples were obtained through the right femoral vein through a disposable bioptome (Bipal, Biosense Webster) using a steerable sheath (Agilis NxT, St Jude Medical). For LV EMB a transseptal approach was implemented. Before biopsy, non-invasive diagnostics were completed according to guidelines recommendations. EMB indication was based on current clinical guidelines.
Results: All patients were extensively evaluated including cardiac magnetic resonance imaging (CMR), [^{18}F]-Fluorodeoxyglucose positron-emission tomography computer tomography (FDG PET-CT) and genetic testing. The three patients were all referred for suspected cardiac sarcoidosis. Based on biopsy results we only initiated immunosuppressive treatment in one patient, in two patients we considered alternative diagnosis. Figure 1 shows an example of a biopsy proven cardiac sarcoidosis.
Conclusion: In the present case series EAM guided EMB proved to be feasible and useful to improve diagnostic accuracy. However, more data is urgently needed. Future studies should systematically evaluate safety, patients' selection, pre- and post-test probability as well as ideally clinical outcomes.

Figure 1:

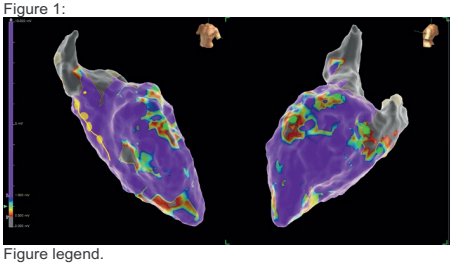

Figure legend.
Electroanatomic voltage mapping with the Advisor HD Grid mapping-catheter (Abbott, USA). Yellow dot indicating the bioptome (Bipal, Biosense Webster). Green dots indicate successful biopsies. Images showing the static (voltage) color-coded maps, purple indicating healthy myocardium and yellow to red representing areas of low voltage.

I.2
LV Dyssynchrony at Rest and Under Stress: A Semi-Quantitative Examination of Heart Failure Patients and Controls via Cardiac MRI

Rebecca Elisabeth Beyer[1,2,3], Patrick Doeblin[1,2,3], Karl Jakob Weiss[1,2,3], Stefanie Wehrhahn[1,2], Matthias Schneider-Reigbert[1,2,3], Moritz Blum[1,2,3], Sebastian Kelle[1,2,3], Djawid Hashemi[1,2,3,4]
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Abstract
Background: Severe left ventricular (LV) dyssynchrony has been identified as a significant prognostic factor for heart failure. Mechanical dyssynchrony can be found even in the absence of electrical dyssynchrony.[1-3] For patients with preserved ejection fraction (HFpEF), cardiac resynchronization therapy (CRT) has shown conflicting results primary endpoints.[4,5] This study aims to assess the advanced image-guided assessment of LV dyssynchrony though strain-based synchronicity index.
Methods: This prospective study enrolled 53 stable chronic HF patients and 19 asymptomatic controls, divided into controls at risk and healthy controls. Its rationale and methods have been previously described.[6] CMR protocol included CINE sequences at rest and under handgrip stress, parametric mapping and late gadolinium enhancement. Volume and function were measured with Medis® Suite MR and strain analysis was done through MyoStrain. For dyssynchrony assessment, AHA-segment strain values were normalized, to mitigate variation in amplitude. Spearman correlation was performed between segments and the mean of correlations was calculated as Synchronicity Index (SI) with higher values (0 - 1.0) indicating more synchronous contraction. Association of SI with EKG, LV remodeling parameters and symptoms was assessed. Mann-Whitney-U was used to compare dyssynchrony between the groups. Statistical significance was accepted at a p-value < 0.05.
Results: Patients with HFrEF (n=18) and HFmEF (n=18) showed the lowest synchronicity index both at rest and under stress, denoting a poor contraction pattern. HFpEF patients (n=17) and controls at risk (n=7) for HF exhibited higher LV dyssynchrony than healthy controls (n=12, 0.85 ± 0.068). Under exercise-induced stress, this dyssynchrony worsened in HFpEF patients (0.67 ± 0.115, p=0.002), but improved in controls at risk (0.71 ± 0.198, p=0.097). This difference persisted after excluding individuals with a QRS>120ms. While QRS duration showed no association, synchronicity index correlated significantly (p<0.001) with NYHA Class (r=-0.39 rest, r= -0.66 stress) and NT-proBNP (r= -0.55 rest, r= -0.48 stress). QRS showed mild correlation with LVEF (r= -0.33, p= 0.004), but correlation of SI and LVEF was strong (r= 0.84 rest, r= 0.88 stress, p<0.001), and slightly higher than the correlation of MyoStrain and LVEF.
Conclusion: Compared to exclusively employing EKG markers, the incorporation of the strain-based Synchronicity Index gives additional insights into dyssynchrony and left ventricular function, with similar performance to strain values. HFpEF patients demonstrated greater LV dyssynchrony compared to healthy controls, which was aggravated by exercise stress. Additional research is required to fully comprehend LV dyssynchrony's mechanisms and therapeutic implications in heart failure and HFpEF especially.

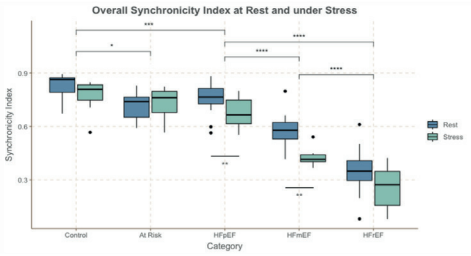

Figure 1 Overall Synchronicity Index at rest and under stress in heart failure patients and controls. Bonferroni-adjusted Mann-Whitney U test was used to calculate difference between groups. HFpEF = Heart failure with preserved ejection fraction. HFmEF = Heart failure with mildly reduced ejection fraction. HFrEF = Heart failure with reduced ejection fraction. p<0.05 = *; p<0.01 = **; p<0.001 = ***; p<0.0001 = ****.

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I.3
Clinical relevance of the "Risk of Heart Disorders" Score from cloud-based heart health analytics of Holter ECG data (Cardiolyse) for development and progression of heart failure

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Introduction: Several markers derived from 12-lead electrocardiogram (ECG) such as prolonged QRS duration and prolonged QT interval are known to be associated with heart failure (HF). However, the predictive value of novel markers exclusively derived from long-term Holter ECG for HF-related clinical outcome compared to established markers NT-proBNP and the HF risk score (Meta-Analysis Group in Chronic Heart Failure (MAGGIC) Risk Score) remains to be further elucidated.
Aim: This project aimed to examine how novel cloud-based Holter ECG analysis predicts adverse events in individuals with HF.
Methods: Data from the MyoVasc study (NCT04064450), a prospective cohort on HF, were analyzed. Subjects underwent a highly standardized 5-hour examination, including a Holter ECG recording. Analysis of ECG data was performed by Cardiolyse, a company specialized in heart health analytics, excluding individuals with permanent pacemaker stimulation and atrial fibrillation. Implementing elastic-net Cox regression models, the most predictive parameter for worsening of heart failure (WoHF) and all-cause death (ACD) was determined. The clinical determinants of this parameter and its relationship to markers of cardiac structure and function were assessed with linear regression models adjusted for sex, age, medication, and comorbidities. Cumulative incidence curves were used to determine clinically relevant cut-off values to identify individuals with an elevated risk of adverse events. Finally, using multivariable Cox regression models adjusted for sex, age, medication, and comorbidities, the most predictive parameter was compared to established markers NT-proBNP and the MAGGIC score.
Results: The analyzed sample included 953 individuals with available Holter ECG data. Symptomatic HF was present in in 522 individuals. Out of the 180 markers analyzed by Cardiolyse, composite parameter Risk of Heart Disorders (RoHD), consisting of ECG time and amplitude parameters, was shown to be most predictive. RoHD was highly associated with diabetes mellitus (β_{est} 0.17 [0.01; 0.33], p=0.04) and diuretics intake (β_{est} 0.57 [0.42; 0.71], p<0.0001). RoHD affected all 3 dimensions of heart function (left ventricular ejection fraction: β_{est} -2.71 [-3.29; -2.12], p<0.0001; global longitudinal strain: β_{est} 1.00 [0.68; 1.31], p<0.0001, and diastolic function assessed by E/e': β_{est} 0.45 [0.15; 0.76], p=0.004). Utilizing cut-off values, RoHD predicted WoHF (hazard ratio per standard deviation (HR_{SD}) 1.33 [1.18; 1.50], p<0.0001) and ACD (HR_{SD} 1.34 [1.18; 1.52], p<0.0001) independently of NT-proBNP and the MAGGIC score.
Conclusion: ECG composite parameter "Risk of Heart Disorders" developed by Cardiolyse predicts cardiac structural and functional changes in individuals with HF. RoHD carries independent information from established markers NT-proBNP and the MAGGIC risk score to predict adverse events.

I.4
Right ventricular dysfunction for prediction of long-term recovery in newly diagnosed heart failure with reduced ejection fraction

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Background: Right ventricular (RV) dysfunction is an independent predictor of survival in patients with heart failure (HF). It is unclear if advanced measures of RV function can be used to forecast long-term left ventricular (LV) recovery in newly diagnosed HF.

Aims: This study aimed to examine the value of RV free wall longitudinal strain (RVFWS) and parameters of RV-pulmonary arterial (PA) coupling in predicting the long-term potential for LV improvement in newly diagnosed HF with reduced ejection fraction (HFrEF).
Methods: The study included patients from the PROLONG-II trial. PROLONG-II is a prospective cohort study that thoroughly analyzed the changes of LV function in patients with newly diagnosed HFrEF receiving wearable cardioverter-defibrillator (WCD) under optimization of medical therapy. For this substudy, RVFWS, tricuspid annular plane systolic excursion (TAPSE), fractional area change (FAC), and RV-PA coupling ratios (RVFWS/systolic pulmonary artery pressure (PASP), TAPSE/PASP and FAC/PASP) at baseline and 3-month follow-up (early follow-up) were examined. Patients with insufficient echocardiography quality for advanced RV analysis were excluded. Study patients were divided into LV improvement and non-improvement groups, defined as an LV ejection fraction (LVEF) of >35% or ≤ 35% at last available follow-up (long-term follow-up).
Results: The study included 260 patients (mean age 57 years, 68% men). The mean follow-up was 31.5 (IQR 18.2-45.4) months. One hundred fifty-one (58%) patients experienced LV improvement in the long-term. Baseline LVEF was severely reduced in both groups (24.5 vs. 23.2%, p=0.143). Early improvement of RV function preceded and predicted LV recovery. No significant differences of RV function were observed at baseline assessment; however, the subgroup of patients without long-term LVEF improvement showed worse RV function at 3-month follow-up (RVFWS -18.47±5.12 vs. -20.89±4.34%, p <0.001, TAPSE 17.37±4.87 vs. 19.69±5.12 mm, p = 0.002, FAC 35.19±9.39 vs. 39.72±8.45%, p <0.001). Worse RVFWS at 3-month follow-up was associated with lower LVEF at long-term (r = -0.26, p <0.001). While no differences in RV-PA coupling markers were observed between the groups at baseline, lower 3-month follow-up RVFWS/PASP, TAPSE/PASP, and FAC/PASP were associated with lower long-term LVEF (r = 0.331, p <0.001; r = 0.323, p <0.001; r = 0.312, p <0.001, respectively). RVFWS/PASP identified RV-PA uncoupling was associated with a higher risk of all-cause mortality (hazard ratio 5.41, 95% confidence interval 1.20-24.34, p = 0.003).
Conclusion: In patients with newly diagnosed HFrEF, RV dysfunction observed during the early follow-up period suggests a lower potential for LV improvement in the long-term.

I.5
Long-term outcomes following explantation of durable left ventricular assist device

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Background: Mechanical unloading during left ventricular assist device (LVAD) support promotes reverse remodeling and myocardial recovery, allowing explantation in selected cases. However, long-term outcome data post-LVAD explantation are limited.
Aim: The primary objective of this study was to analyze clinical characteristics and long-term outcomes among patients who underwent LVAD explantation.
Methods: A retrospective analysis of our institution's database was conducted to identify LVAD-supported patients who underwent LVAD explantation or decommissioning between 2004 and 2022. Patients with biventricular assist-device and those with follow-up in an affiliated hospital were excluded. Primary outcomes were all-cause mortality, heart transplantation, and LVAD reimplantation.
Results: Twenty-six patients (mean age 48 years, 81% male) underwent LVAD explantation and were included in the analysis. Non-ischemic cardiomyopathies (69%) were the main heart failure (HF) causes. The median duration of device support was 530 (IQR 262-765) days. Indications for LVAD explant included myocardial recovery (62%), LVAD thrombosis (23%), LVAD infection (8%), palliation and mechanical complications (1 patient each). The mean left ventricular ejection fraction (LVEF) at explant was 42 (IQR 29-51) %. Complete LVAD explantation was performed in 27%, decommissioning in 35%, and plug-based explantation in 39% of patients. During the mean follow-up of 597 (IQR 106-2357) days seven (27%) patients had died, three (12%) were transplanted, two (8%) underwent LVAD reimplantation. Fifteen (58%) patients remained stable during the follow-up of 686 (IQR 169-1379) days. There were no significant differences in age (50 vs. 47 years, p=0.52), gender distribution (87 vs. 73% male, p=0.62), LVEF at explantation (45 vs. 36%, p=0.12), LVAD support duration (451 (IQR 250-647) vs. 565 (IQR 300-988) days, p=0.33), NT-proBNP levels (306 (IQR 155-2089) vs. 601 (IQR 462-4670) ng/l, p=0.41), and laboratory parameters indicating secondary organ damage (aspartate transaminase 24 (IQR 16-32) vs. 26 (IQR 25-40) U/l, p=0.24, alanine transaminase 19 (IQR 13-34) vs. 23 (IQR 14-37) U/l, p=0.49, total bilirubin 9 (IQR 5.8-15.5) vs. 13 (IQR 6.8-26.5) µmol/l, p=0.31, creatinine 93 (IQR 82-124) vs. 88 (IQR 53-140) µmol/l, p=0.41) between patients who maintained stability after explantation and those who experienced recurrence of HF or died. No significant differences were observed in the indications for LVAD explantation between the groups (all p>0.05).
Conclusion: Among patients undergoing LVAD explantation, two-thirds remained stable over the long-term, while one-third experienced worsening of HF, requiring LVAD reimplantation, transplantation, or resulting in death. Novel approaches are needed to accurately identify patients who will remain free of HF recurrence after LVAD explant.

I.6
Epigenome-wide association study of heart failure uncovers phenotype-specific DNA methylation

Mykhailo Krolevets[1, 2, 3], Vincent ten Cate[1, 4, 5], Jürgen H. Prochaska[1, 4, 5], Andreas Schulz[1], Steffen Rapp[1, 4], Elif Yapici[1,3], Stefan Tenzer[6], Miguel A. Andrade-Navarro[7], Steve Horvath[8], Christof Niehrs[2], Philipp S. Wild[1, 3, 4, 5]
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Introduction: Heart failure (HF) is a disease with severe morbidity and poor prognosis. The role of DNA methylation (DNAm) in the progression and development of phenotypes of heart failure is unclear.
Aim: To investigate the importance of individual CpG site methylation in the development and progression of three HF phenotypes, as well as their role in aging processes.
Methods: Individuals with symptomatic HF (universal definition stage C/D, including HFpEF, HFmrEF and HFrEF) of the MyoVasc cohort (N=3,289; NCT04064450) and individuals without cardiovascular disease (CVD) from a population-based cohort (Gutenberg Health Study, N=18,700) were investigated.

DNA was extracted from peripheral blood. DNAm was measured using the Illumina Infinium methylationEPIC v2.0 methylation array (San Diego, USA). Epigenetic age was modeled with GrimAge. Multivariable logistic regression models adjusted for cardiovascular risk factors (CVRFs) were used to assess the relationship between individual CpG sites and each HF phenotype. Ridge regression was used to generate phenotype-specific CpG-scores. Linear regression was used to estimate associations between each HF phenotype CpG score and cardiovascular traits. Cox regression was used to relate CpG scores to clinical outcome. Premature aging was derived using residuals from linear regression of chronological against epigenetic age. Worsening of heart failure was defined as a combination of cardiac-related deaths, hospitalizations resulting from heart failure and progression from stage B to C/D, over 4 years of follow-up, assessed by telephone interviews and by querying medical records.
Results: Data from 1,002 with symptomatic HF and 702 CVD-free individuals were analyzed. After FDR adjustment 104,840 CpG sites were significantly differentially methylated in HFpEF, 57,825 in HFmrEF,113,769 in HFrEF. Only 24.9% of CpG sites were shared between 3 phenotypes. Dyslipidemia (ß=-0.10 [-0.19- -0.01], p=0.038) and family history of MI or stroke (ß=-0.11 [-0.19- -0.03], p=0.008) were negatively associated with the HFpEF score. The strongest association was observed between the HFmrEF score and left ventricular ejection fraction (ß =0.24 [0.05- 0.43], p=0.01). All scores were correlated with premature aging derived from GrimAge (all p<0.001). The HFrEF score outperformed GrimAge in prediction of all-cause mortality and worsening of HF. This score shared fewer than 15% of GrimAge CpGs.
Conclusion: A large number of CpG sites were identified to be associated with all 3 HF phenotypes vs CVD-free individuals. Phenotype scores generated with these CpGs were strongly associated with multiple CVD-related traits, as well as with clinical outcome. Between-phenotype differences were observed on individual CpG as well as on the score-level.

I.7
The role of MRAS in atherosclerosis and relevant cardiovascular risk factors

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A study by Erdmann *et al.* in 2009, revealed a region on 3q22.3, which encompasses the *MRAS* gene as a risk factor for Coronary Artery Disease (CAD). *MRAS* encodes muscle Ras, a member of the Ras family of small membrane associated GTPases associated with TNF-α signaling. According to GTEx and other eQTL datasets, *MRAS* risk variants for CAD increase *MRAS* mRNA levels primarily in the arterial tissue. Moreover, recently it has been indicated that functional *MRAS* variants are Macrophage- and SMC-specific. The role of *MRAS* in atherogenesis is still elusive. Therefore, we aimed to study the function of *MRAS* in vascular smooth muscle cells (SMCs), one of the key cell types in the etiology of atherosclerosis and in plaque stabilization. To assess the impact of *MRAS* deficiency, human primary aortic SMCs transfected with MRAS-specific siRNA and murine aortic SMCs derived from Mras/Apoe knockout (ddKO) mice were subjected to functional assays including proliferation and migration. Mras/Apoe ddKO murine SMCs significantly proliferate more and migrate faster as compared to wild type SMCs when stimulated with TNF-α (n=4, p<0.001), but not without stimulation. Similar results were obtained from human SMCs after TNF-α stimulation where the knockdown of *MRAS* increases migration and proliferation (n=6, p<0.01). Control experiments with PDGF stimulation showed no impact of *MRAS* deficiency on cellular behavior, indicating that *MRAS* is specific to TNF-α signaling. In conclusion, *MRAS* deficiency modulates SMC biology in response to TNF-α. However, further studies are needed to decipher its exact role in plaque stability.
Keywords: MRAS, TNF-α

I.8
Optical measurement of Zincprotoporphyrin, a novel non-invasive method to detect iron deficiency

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Background: Iron deficiency (ID) is a frequent comorbidity in heart failure (HF) associated with adverse outcomes. Although the European Society of Cardiology (ESC) HF Guidelines recommend periodic screening with serum markers of systemic ID, iron deficiency still is underdiagnosed and undertreated. Erythrocyte zinc protoporphyrin (ZnPP) is an established indicator of ID, formed when iron availability is limited during haematopoiesis. Here, we prospectively evaluated a novel optical method to non-invasively measure ZnPP in patients with HF.
Methods: We enrolled 341 consecutive patients with symptomatic heart failure. ZnPP was optically measured on the mucosa of the lower lip. According to the literature, we considered ZnPP cut-off >70 µmol/mol haem indicative of ID. For comparison, we performed direct measurement in the blood and examined conventional serum parameters of ID and clinical characteristics. We further examined quality of life, functional status, and mortality.
Results: Non-invasive measurement yielded a median ZnPP concentration of 33 (IQR 26-42) µmol/mol haem. ZnPP concentration was closely correlated to all iron-related serum parameters (all p<0,0001). Patients with a ZnPP concentration >70 µmol/mol haem had a positive predictive value of 93% for ID, as defined by the recent ESC HF Guidelines. Further, patients with ZnPP concentration >70 µmol/mol haem showed increased HF severity, indicated by higher serum biomarkers,, as well as impaired quality of life and functional status. Notably, in our HF cohort a ZnPP concentration >70 µmol/mol haem was associated with an increased mortality of all cause.
Conclusion: ZnPP concentration can be measured with a novel optical method and is strongly related to established markers of systemic iron status, disease severity, and poor outcome in heart failure patients. This optical method potentially provides a rapid, easy-to-use means for point-of-care diagnostics for ID in HF.

I.9
Angiotensin receptor-neprilysin inhibition improves ventricular-arterial coupling in patients with heart failure and reduced ejection fraction

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Background: Sacubitril/valsartan reduces heart failure (HF) hospitalizations and cardiovascular mortality in patients with HF and reduced ejection fraction (HFrEF). These beneficial clinical effects of angiotensin receptor-neprilysin inhibition on left ventricular (LV) myocardial function are incompletely understood.
Purpose: This study aimed to analyze the changes in left ventricular end-systolic elastance (Ees; a measure of LV contractility), effective arterial elastance (Ea; a measure of afterload), and the ventricular-arterial coupling ratio (Ea/Ees)

after starting treatment with sacubitril/valsartan in patients with HFrEF.

Methods: From April 2020 to November 2021, 117 consecutive patients with symptomatic HF and left ventricular ejection fraction (LVEF) <40% in whom treatment with sacubitril/valsartan was initiated were prospectively enrolled across two centers in Germany. Transthoracic echocardiography with simultaneous arm-cuff blood pressure measurements was used for non-invasive pressure-volume loop analyses. The primary endpoints were changes in Ees, Ea, and the Ea/Ees ratio after six months of sacubitril/valsartan treatment. The study is registered with ClinicalTrials.gov, NCT04498780.

Results: Mean age was 65±13 years and 30% were female. The etiology of HF was ischemic in 54.7% and non-ischemic in 45.3% of the patients. 102 patients with complete baseline and follow-up data were included in the pressure-volume loop analyses. Among those, 62% were on the target dose of sacubitril/valsartan. After six months, Ees increased (0.66 mmHg/ml [IQR 0.45-0.94] vs. 0.78 mmHg/ml [IQR 0.57-1.10], p=0.001) and Ea decreased (1.76 mmHg/ml [IQR 1.48-2.13] vs. 1.62 mmHg/ml [IQR 1.36-1.96], p=0.014). Hence, the Ea/Ees ratio was improved (2.52 [IQR 1.88-4.05] vs. 1.93 [IQR 1.50-2.63], p<0.001), *Figure 1*. LV end-diastolic pressure, LV end-diastolic and end-systolic volumes were reduced, and LVEF increased from 33% to 43%, p<0.001, respectively. The percentage of patients with NYHA class III changed from 25.6% to 5.9%, the median NT-proBNP level decreased from 1770 pg/ml (IQR 805-5374) to 724 pg/ml (IQR 298-1600), and the mean 6-minute walking distance increased from 371 m (±125) m to 423 m (±122), p<0.001, respectively.

Conclusion: After six months of treatment with sacubitril/valsartan, patients with heart failure and reduced ejection fraction presented with increased LV contractility, reduced afterload, and improved ventricular-arterial coupling. Beyond reverse LV remodeling, improved ventricular-arterial interaction may contribute to the favorable mid-term outcome of sacubitril/valsartan treatment in heart failure with reduced ejection fraction.

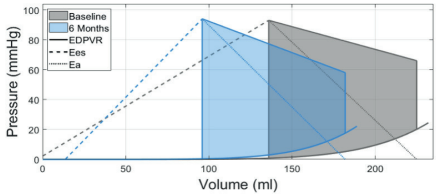

Figure 1. Exemplary presentation of the non-invasive pressure-volume loops from one representative patient at baseline (grey) and after six months (blue) of treatment with sacubitril/valsartan. EDPVR = end-diastolic pressure-volume relationship; Ees = end-systolic elastance; Ea = arterial elastance.

I.10

ESCAPE - eine EU-weite Multicenterstudie zur "Evalation of a patient-centred biopsychoSocial blended Collaborative care Pathway for the treatment of multimorbid Elderly patients"

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Hintergrund: Multimorbide Patient*innen werden normalerweise von ihre*r Hausärzt*in und weiteren Fachärzt*innen behandelt mit oft eher kurzen Kontaktzeiten und ausbaufähiger Vernetzung der beteiligten Personen. Wir erwarten, dass eine bessere Verständigung zwischen Patient*innen, Angehörigen und Ärzt*innen Gesundheit und Wohlbefinden der Patient*innen steigern können.

Hypothese: Die Regelversorgung älterer multimorbider Patient*innen mit Herzinsuffizienz ergänzt um eine optimierte und abgestimmte *Blended Collaborative Care (BCC)-Intervention*[1-4] ist der Regelversorgung allein hinsichtlich der Verbesserung gesundheitsbezogener Lebensqualität (HR-QoL) überlegen.

Methoden: Prospektive Kohortenstudie mit integriertem *Randomised Controlled Trial* (RCT).

Einschlusskriterien: ab 65 Jahre, diagnostizierte Herzinsuffizienz, ≥ 2 weitere somatische Erkrankungen, psychische Belastung (HADS-Gesamtscore >12 und/oder Psychdiagnose). 1:1-Randomisierung stratifiziert nach Geschlecht, Gebrechlichkeit und Land. *Orte:* Göttingen, Köln, Leipzig, Hamburg. Odense, Roskilde, Slagelse. Dublin. Kaunas. Budapest. Bologna.

Intervention: Über 9 Monate regelmäßige Betreuung von Patient*innen durch fachkompetente, geschulte „Care Manager*in (CM)" anhand eines mit Hausärzt*in und Patient*in erstellten Behandlungsplans, der - orientiert am Meta-Algorithmus für Multimorbidität (MAM)[5] - die wichtigen

medizinischen Gesichtspunkte inklusive „Red Flags“ (kritische Symptome, die rechtzeitig medizinisch behandelt werden müssen) sowie Präferenzen, Werte und Lebensziele der Patient*innen berücksichtigt.
Ziele: Überwachung medizinischer Parameter. Emotionale Unterstützung. Unterstützung beim Aufbau gesundheitsförderlichen Verhaltens (Medikamentenadhärenz, Lebensstil, Sozialkontakte etc).Die Intervention erfolgt unter regelmäßiger Supervision der CM durch ein Team aus Fachkolleg*innen (Kardiolog*in, Allgemeinmediziner*in, Psychosomatiker*in, Pharmakolog*in), gestützt von der studieneigenen elektronischen Patientenakte imergo®.
Erhebungszeitpunkte: Baseline, 9 Monate, 18+ Monate

- **Primärer Endpunkt:** gesundheitsbezogene Lebensqualität (HRQoL) anhand des EQ-5D-5L
- **Objektive sekundäre Endpunkte:** Hospitalisierung, Morbidität, Gesamtmortalität. Kosteneffizienz, Kosten-Nutzen-Verhältnis.
- **Subjektive sekundäre Endpunkte:** Depressivität, Ängstlichkeit, Krankheitsspezifische Lebensqualität, kognitive Beeinträchtigung, Gebrechlichkeit, Aktivitäten des täglichen Lebens, körperliche Funktion und Aktivität, Erwartungen an die Behandlung, Schlafprobleme, Schmerzen/Beschwerden, Belastung durch die Behandlung, Belastung der informellen Pflegepersonen, emotionale Unterstützung.

Analyse des RCT nach dem Intention-to-treat-Prinzip. Die Endpunkte werden mittels Kovarianzanalyse (ANCOVA) analysiert, die jeweiligen Ausgangswerte bei Baseline dienen als Kovariaten und die Stratifikationsvariablen der Randomisierung als Faktoren. Gesundheitsökonomische Evaluation.
Ergebnisse: Nach erfolgreicher Machbarkeitsstudie mit dreimonatiger Intervention und 10 Patient*innen wurden seit April 2023 135 von geplanten 300 Patient*innen in den RCT rekrutiert. Das Studienprotokoll wurde kürzlich publiziert [6].
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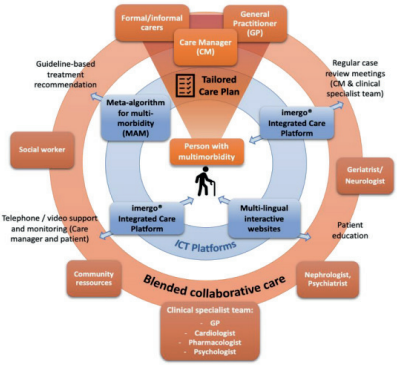

Figure 1: Overview of the enhanced BCC approach used in ESCAPE

I.11
Functional capacity and incidence of sarcopenia in older heart failure patients undergoing inpatient cardiac rehabilitation – an observational cohort study

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Introduction: Sarcopenia is highly prevalent in patients with heart failure (HF).[1] Cardiac rehabilitation (CR) can improve clinical outcomes in patients with HF. It is unclear whether sarcopenic HF patients attending CR experience a change in their status after CR.
Purpose: Aim of this prospective cohort study was to assess the functional capacity and frailty at baseline as well as the incidence of sarcopenia in HF patients during inpatient CR versus three months follow-up.
Methods: This is an observational cohort study of the ongoing randomized, controlled, multicenter prehabilitation study “PRECOVERY”[2]. Recruitment was carried out in four inpatient rehabilitation clinics. Inclusion criteria: patients ≥ 75 years receiving inpatient CR following a cardiac procedure (e.g., coronary artery bypass [CABG] surgery). HF was recorded as a binomial variable at baseline. This subgroup analysis focuses only on results of HF patients. We used the Strength, Assistance with walking, Rise from a chair, Climb stairs and Falls (SARC-F) questionnaire to identify probable sarcopenic

patients at baseline (SARC-F score ≥ 4 indicates sarcopenia). The Clinical Frailty Scale (CFS), Katz-Index and hand grip strength (HGS) assessed frailty. Short Physical Performance Battery (SPPB) and six-minute-walk test (6MWT) measured functional capacity. Three months after baseline, the SARC-F questionnaire was repeated by telephone. To analyze the results of the pre-post test, the Wilcoxon signed-rank test was applied.
Results: A sample of 88 HF patients (79.9±4.3 years; 56% males) completed the baseline assessments. Main indications for CR were valve replacement or reconstruction (35%) and CABG surgery (21%). At baseline, 43% were defined as frail (CFS ≥ 4) and 37% had a SARC-F score ≥ 4 (sarcopenia). Other baseline assessments of the sample were (mean±SD) Katz-Index 5.6±0.9, HGS 23.9±9.5 kg, SPPB Score 7.1±3.4 and 6MWD 270.0±144.6 m. In the total HF sample (n = 88), no significant changes were observed in the SARC-F score (3.0±2.1 vs. 2.6±2.1, p = 0.137). At follow-up, 31% of all HF patients showed a score ≥ 4 in SARC-F (sarcopenia). However, in the sub-group of HF patients (n = 34) with sarcopenia at baseline, 57% improved after three months. The pre-post comparison for this entire sub-group shows a significant positive change (n = 34, 5.3±1.3 vs. 4.3±1.8, p = 0.028).
Conclusion: The incidence of sarcopenia in older HF patients entering CR is high and still high at follow-up. Participation in aftercare programs such as cardiac training groups (phase III) seems to be essential to counteract this development.
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I.12
Proteomic profile of chronotropic incompetence reveals differences in the heart failure phenotypes

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Introduction: Chronotropic incompetence (CI), defined as the inability to raise HR to satisfy metabolic demands during exercise, is related to adverse clinical outcome in heart failure (HF). However, pathophysiological mechanisms are poorly understood and appear to differ between HF phenotypes.
Aim: The aim of the project was to uncover molecular mechanisms of CI in HF.
Methods: Data from the MyoVasc study (NCT04064450), a prospective cohort on HF, were analyzed. Subjects underwent a highly standardized 5-hour examination, including cardiopulmonary exercise testing (CPET) on a cycle ergometer and deep clinical phenotyping. Subjects achieving maximum exertion (respiratory exchange ratio>1.0) were included for analysis. Predicted heart rate reserve derived from CPET was used as a measure of CI. A total of 358 proteins, quantified via immuno-PCR targeted proteomics (Olink, Uppsala, Sweden), were used as predictors to identify a protein signature of CI with elastic-net linear regression adjusted for sex and age. To determine clinical relevance of the CI signature, a proteomic score derived from the proteins identified for CI was used in Cox regression models. Protein signatures of CI in the HF phenotypes according to left ventricular ejection fraction (≥50 [PEF] vs <50% [REF]) were similarly determined. Enrichment analyses were performed with the STRING database to gain further insight into pathophysiological molecular mechanisms of CI.
Results: The analysis sample included 886 subjects (median age 63 years [interquartile range 55;72]; 29.9% women). Symptomatic HF stage C/D was present in 42.8% of the subjects (PEF, n=151; REF, n=218). A total of 58 proteins were related to CI in the analysis sample. Enrichment analysis identified processes such as inflammation, neuronal cells activation, and angiogenesis participating in CI. The CI protein signature predicted all-cause death (hazard ratio per SD 2.12 [1.85;2.43], p<0.0001) and worsening of HF (HR_{SD} 1.59 [1.39;1.81], p<0.0001), independently of age, sex, cardiovascular risk factors and comorbidities. A total of 29 and 54 proteins were related to CI in HF with PEF and REF, respectively, with six proteins common to both phenotypes. Processes in REF were linked to neuron apoptic processes, endothelial cell morphogenesis and atherosclerosis. Processes in PEF mostly concerned white
blood cell chemotaxis.
Conclusion: The protein signature of CI uncovered systemic mechanisms related to the vascular and nervous system. The proteins identified for CI in strongly differed the HF phenotypes, denoting novel distinct potential molecular mechanisms of CI. These different mechanisms of CI in HF have implications for risk stratification and intervention.

I.13
Lebensqualität und psychologische Aspekte bei Patienten und ihren Angehörigen nach überlebter ECMO Therapie

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Hintergrund: Extrakorporale Membranoxygenierung (ECMO) wird zunehmend bei therapierefraktärem kardiogenem Schock eingesetzt. Während der Behandlung sind die Patienten und ihre Angehörigen verschiedenen Stressoren ausgesetzt, die den psychischen Zustand auch längerfristig beeinflussen können. Dies kann zur verminderten gesundheitsbezogenen Lebensqualität (HRQoL), Angst- und Depressionssymptomatik oder posttraumatischen Belastungsstörung (PTBS) führen.
Methodik: Aus dem Zeitraum 1. Januar 2018 bis 31. Dezember 2020 wurden konsekutiv 119 Patienten in die Studie eingeschlossen, die eine ECMO-Implantation in der Klinik für Herz-, Thorax- und Gefäßchirurgie der Universitätsmedizin Göttingen erhalten hatten. Die Überlebenden und ihre

Angehörigen wurden mittels verschiedener Fragebögen zu ihrem psychischen Befinden und ihrer Lebensqualität befragt: HRQoL mit EQ-5D-5L, EQ-5D-VAS, Disstress durch PSS-4, PTBS mit PTSS-14 und Resilienz mit RS-13. Darüber hinaus wurde Angst und Depression mit HADS ermittelt und die Spiritualität mit der Spiritualitätsskala des QoL-VAD.
Ergebnisse: 58 (48,7%) Patienten wurden erfolgreich von der ECMO entwöhnt und 24 (20,2%) Patienten konnten aus dem Krankenhaus entlassen werden. Bis zum Zeitpunkt der Nachverfolgung im April 2021 verstarben vier weitere Patienten, sodass sich das Kollektiv auf 20 Patienten beläuft. Von diesen beantworteten 16 Patienten und 15 Angehörige die Fragebögen. Die Überlebenden der ECMO-Therapie zeigten eine verminderte HRQoL im EQ-5D-5L (Median (Md) 39,9; Interquartile Range (IQR) 22-64,1), EQ-5D-VAS (Md 50; IQR 26,3-53) und HeartQoL (Md 1,3; IQR 1-1,8). Mittels HADS konnte bei 62,5% der Überlebenden ein erhöhter Wert für Depressivität (Cut-off ≥ 8) und bei 56,3% vermehrte Angstsymptomatik (Cut-off ≥ 8) evaluiert werden. Disstress wurde anhand PSS-4 mit einem Median von 9,5 (IQR 5,3-13) ermittelt. 81,3% zeigten eine verminderte Resilienz und niedrige Spiritualität (Md 57,5; IQR 35-75). Ein erhöhter Wert in PTSS-14 lässt bei 43,7% der Überlebenden und bei 53,3% der Angehörigen eine PTBS vermuten. Gleichermaßen weisen 53,3% der Angehörigen erhöhte Angstsymptomatik (HADS-A ≥ 8) und 20% depressive Symptome (HADS-D ≥ 8) auf. Auch die HRQoL zeigt sich bei ihnen vermindert. Der EQ-5D-5L liegt hier im Median bei 54,4 (IQR 39,9-72,8) und EQ-5D-VAS bei 80 (50-89).
Zusammenfassung: Sowohl die Überlebenden der ECMO-Therapie, als auch ihre Angehörigen zeigten vermehrt eine depressive und Angstsymptomatik, posttraumatischen Stress, Disstress und eine verminderte HRQoL. Ebenso wurde eine geringe Resilienz und Spiritualität festgestellt. Größere Studien sollten den Einfluss der ECMO-Therapie auf psychische Faktoren von Überlebende und ihren Angehörigen weiter untersuchen. Unsere Studienergebnisse zeigen auf, dass ein Screening der Patienten und der Angehörigen sinnvoll sein kann, um diejenigen zu identifizieren, die von einer psychologischen Unterstützung profitieren könnten.

I.14
Die Symptomlast gemessen an der NYHA-Klasse ist ein unabhängiger Faktor für Pruritus bei Patienten mit Herzinsuffizienz

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Hintergrund: Pruritus ist ein unangenehmes Symptom, welches die Lebensqualität von Patienten stark beeinflusst. Bereits in der Vergangenheit konnte gezeigt werden, dass Patienten mit chronischer Herzinsuffizienz (CHF) häufig unter Pruritus leiden. Ursachen und Risikofaktoren von Pruritus bei CHF-Patienten sind unbekannt. Ziel dieser Studie war es, Risikofaktoren für Pruritus bei Patienten mit chronischer Herzinsuffizienz zu identifizieren.
Methoden: Für diese monozentrische, prospektive Kohortenstudie wurden CHF-Patienten rekrutiert. Aspekte der Pruritus-Symptomatik wurden mittels eines dermatologischen Fragebogens erfragt. CHF-Symptome, Komorbiditäten, Medikation und Laborwerte wurden ebenfalls erfasst und im Hinblick auf eine Assoziation mit dem Auftreten oder der Intensität des Pruritus analysiert.
Ergebnisse: Daten von 550 CHF-Patienten (HFrEF 44,7%, HFmrEF 20,9%, HFpEF 34,4%; mittleres Alter 71,3±15,7 Jahre, 30,4% weiblich) wurden analysiert. 25,3% der Patienten berichten häufig (3-5x/Woche), oft (1-2x/Woche) oder täglich an Pruritus zu leiden. Patienten in höheren NYHA-Klassen (NYHA III + IV) hatten signifikant häufiger Pruritus im Vergleich zu niedrigeren NYHA-Klassen (NYHA I + II) (31,2% vs. 21,1%, p=0.024). Patienten mit Pruritus waren häufiger weiblich (p=0,025), litten vermehrt an einer begleitenden Stauungsdermatitis (p=0,026), an chronischen Lungenerkrankungen (p=0,014) und hatten niedrigere Hämoglobinwerten (p=0,002) und höhere Leukozytenzahlen (p=0,004). Andere Parameter, die die Herz-, Leber-, Nieren-, und Schilddrüsenfunktion sowie medizinische Therapien widerspiegeln, zeigten bei Patienten mit und ohne Pruritus keine signifikanten Unterschiede (alle p>0,05). In der multivariaten logistischen Regressionsanalyse behielten nur die NYHA-Klasse (OR 1,55, 95% Konfidenzintervall [95%CI] 1,09-2,20, p=0,016) und eine erhöhte Leukozytenzahl (OR 1,11, 95%CI, 1,03-1,21 p=0,007) ihre prädiktive Aussage für das Auftreten von Pruritus bei CHF-Patienten.
Schlussfolgerung: Die NYHA-Klasse und die Leukozytenzahl sind unabhängige Prädiktoren für das Auftreten von Pruritus bei CHF-Patienten. Aufgrund der erheblichen Beeinträchtigung der Lebensqualität, sollte Pruritus bei der Behandlung dieser Patienten frühzeitig berücksichtigt werden. Der prognostische Wert von Pruritus bei Patienten mit CHF muss weiter analysiert werden.

I.15
Excess RAS activation is attributed to the combination of forward and backward failure in heart failure with reduced ejection fraction.

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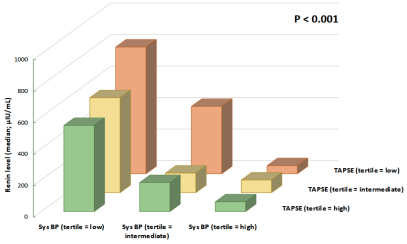
Rationale & Aim. Regulation of the renin-angiotensin-system (RAS) in heart failure with reduced ejection fraction (HFrEF) still raises questions, as a large proportion of patients show normal renin levels despite manifest disease. On the one hand, renin secretion by the kidneys is mainly regulated by renal perfusion pressure and sodium levels, and on the other hand, especially right ventricular (RV) impairment is associated with poor outcomes in HFrEF. When combining the two mechanisms in experimental studies, venous congestion results in reduced renal perfusion pressures and stimulates renin secretion. We hypothesized that excess renin levels are mainly a result of right ventricular failure as a sequalae of left ventricular dysfunction. The study aimed to link right ventricular function (RVF) with renin levels and to investigate further contributors to excess RAS activation.
Methods. 332 chronic HFrEF patients on timely optimal medical heart failure therapy undergoing routine ambulatory care were consecutively enrolled in a prospective, registry-based, observational study. Laboratory parameters, including cardiac specific markers renin, aldosterone and NT-proBNP, comprehensive echocardiographic examination (n=247), and right heart catheterization (n=85) were documented. The relationship of renin with the respective parameters and outcome was analysed.
Results. Renin concentration was not associated with NYHA class, or NT-proBNP. Systolic blood pressure, systemic vascular resistance, serum sodium, aldosterone and LDH were associated with increased renin levels (p<0.035, for all). Renin levels similarly increased with worsening of RVF parameters as FAC, TAPSE, TDI, and IVC diameter (p<0.011 for all), but not with pulmonary pressure. Excess renin levels were observed when worsening RVF was combined with reduced renal perfusion [625µIU/ml(IQR:182–1761) vs 67µIU/ml(IQR:16–231), p<0.001] (*Figure 1*) which was associated with worse survival.

Conclusion. Whilst unrelated to classical indices of HF severity, circulating renin levels increase with worsening of RVF and, in particular, when the combination of forward and backward failure is present. This might explain normal renin levels in HFrEF patients but also excess renin levels at poor hemodynamic state.

Figure 1. Renin concentration as a function of forward- and backward-failure. 3D histogram
illustrating the triangular relationship between renin, systemic blood pressure and right ventricular function.
Data were compared by Kruskal-Wallis test.
SBP – systolic blood pressure; TAPSE – tricuspid annular plane systolic excursion



II.1
Cardioprotective actions of SGLT2 inhibitors through regulation of EndMT and fibrosis

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Background: The cardiovascular benefits of sodium glucose co-transporter 2 inhibitors (SGLT2is) have been demonstrated in several clinical trials. Especially Dapagliflozin (DAPA) and Empagliflozin (EMPA) significantly reduce cardiovascular (CV) adverse events in heart failure patients. However, the full spectrum of cardio-protective mechanisms of SGLT2is has not been elaborated yet, still limiting their use in clinics. While an interference with ion homeostasis in cardiomyocytes has been shown, the impact of these drugs on other important cell types in the CV environment, in particular endothelial cells and fibroblasts, remains largely undefined.
Methods and Results: We investigated DAPA and EMPA in human umbilical vein endothelial cells (HUVECs) stimulated with an endothelial to mesenchymal transition (EndMT) inducing cocktail in vitro. Assessment of mesenchymal marker expression with quantitative real time polymerase chain reaction suggested a downregulation of EndMT through DAPA and EMPA. Reversal of mesenchymal activation was also accelerated with SGLT2i application. Not only on a gene expression level but also in terms of cellular morphology, SGLT2is influenced the transition from endothelial cell shapes to fibroblast-like structures. In line, we observed inhibitory activity of DAPA on primary human cardiac fibroblast (HCF) proliferation as well as migration in scratch wound assays. Transcriptional profiles of HCFs exposed to SGLT2is represented functional phenotypes as cell migration and proliferation associated genes were dysregulated. In contrast to the EndMT setup, we could not observe an influence of DAPA or EMPA on pro-fibrotic signaling in general in the HCF context.
Conclusion: We assessed the impact of SGLT2is on endothelial cell biology applying *in vitro* EndMT assays in HUVECs. Our findings underline a modulation of mesenchymal activation of endothelial cells. In line, we found quiescing activity of DAPA on HCFs as their migratory and proliferative capacity dwindled. Based on these findings, we speculate that cardioprotective effects of SGLT2is are in part mediated through inhibition of excessive fibrotic signaling and adverse remodeling.

II.2
Factors Limiting Optimal Medical Therapy only concern a fraction of advanced HFrEF patients and might improve over time

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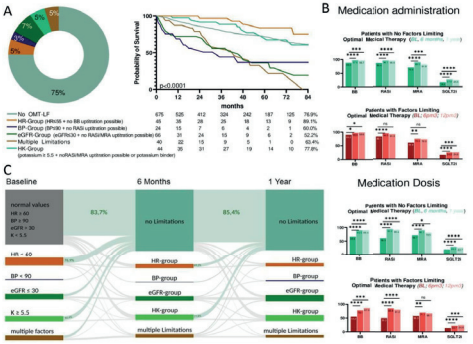
Introduction: Quadruple therapy, called optimal medical therapy (OMT), involving renin-angiotensin system inhibitors (RASi), beta-blockers (BB), mineralocorticoid receptor antagonists (MRA), and sodium glucose cotransporter 2 inhibitors (SGLT2i), has demonstrated mortality reduction in Heart Failure with reduced Ejection Fraction (HFrEF). However, barriers in OMT implementation persist. This study examines OMT limiting factors (OMT-LF) and their change over time.

Methods: This study included 900 stable HFrEF patients from a prospective registry, focusing on advanced HFrEF. Out of these, 264 patients had available data for longitudinal assessment. Patients were categorized into groups based on OMT-LF at baseline (BL) and follow up at 6 and 12 months: HR-group (heart rate ≤ 55 bpm + submaximal BB dosage), BP-group (systolic blood pressure ≤ 90 mmHg + submaximal RASi dosage), eGFR-group (estimated glomerular filtration rate ≤ 30 ml/min/1.73m² + submaximal RASi/MRA dosage), and HK-group (potassium levels ≥ 5.5 + submaximal RASi/MRA dosage with/without
potassium binder).
Results: BL demographics showed mostly male patients (76.3%) with a median NT-proBNP of 1951 pg/mL (IQR: 813-4327) and NYHA classes I/II/III/IV at 11.8%/44.0%/39.8%/1.3%. At BL, 75.2% showed no OMT-LF and were therefore eligible for uptitration. Among patients with OMT-LF, the eGFR group (7.4%) was the most common, followed by the HR-group (5.0%), HK-group (5.0%), multiple OMT-LF (4.6%), and the BP-group (2.8%). Patients with OMT-LF had more severe HF (NT-proBNP 2625 pg/ml [IQR: 1125-6325] vs. 1817 pg/ml [IQR: 753-3830], p<0.0001). The eGFR, BP, or multiple OMT-LF group had the
worst survival rates (p < 0.0001), while the HR-group and HK-group had comparable survival rates to patients without OMT-LF (**A**). There was a significant increase in medication use and dosage, especially within the first 6 months, regardless of the presence of OMT-LF (**B**). Overall, the proportion of patients receiving individual maximum HF therapy increased to 45.1% from 14.4% at 6 months (p<0.0001). The distribution of OMT-LF remained similar at each time point; there was however a substantial crossover between OMT-LF groups, potentially indicating worsening but also recovery from OMT-LF (**C**).
Conclusion: This study demonstrates the feasibility of implementing OMT in advanced HFrEF in a real-world setting. Despite advanced disease, only 25% of patients displayed OMT-LF, and therapy could be significantly up-titrated in all patient groups. Crossovers between OMT-LF suggest that OMT-LF are not strictly tied to an individual patient's journey. These findings support continuous discussions on strategies for improved treatment implementation in HFrEF.

FIGURE A. Distribution and outcome of OMT-LF. The distribution of OMT-LF in our cohort is shown as a donut chart. The
association with all-cause-mortality is shown as Kaplan-Meier plots for individual groups. For the Kaplan-Meier plot the difference between groups was assessed by the log rank test. **B. Timely change in medication administration (yes/no, up) and medication Dosis (≥50%), down) between BL, 6 months and 1 year.** The percentage of patients receiving specific HF medication/dosis ≥50% at BL, 6 months and 1 year is shown as bar diagram. The percentage is plotted within the bar. The nonparametric Wilcoxon matched-pairs signed rank test was used for comparisons between groups, p<0.05 was considered significant. **C. OMT-LF over 1 year.** Longitudinal evolution of OMT-LF from baseline to FUP (6 months and 1 year). Only patients with available data for BL, 6 months and 1 year were included (n=264).



OMT-LF – Optimal Medical Therapy Limiting Factors; HR – Heart Rate; BB – Beta-Blocker; BP – Blood Pressure; RASi – Renin-Angiotensin-System- Inhibitor; eGFR – estimated Glomerular Filtration Rate; MRA – Mineralocorticoid Receptor Antagonist; HK – Hyperkalaemia; HR-group: HR≤55 bpm + BB therapy at submaximal dosages - BP-group: s BP≤90mmHg + RASi therapy at submaximal dosages - eGFR-group: eGFR≤30ml/min/1.73m2 + RASi/MRA therapy at submaximal dosages - HK-group: HK (K≥5.5) +RASi/MRA therapy at submaximal dosages or potassium binder - multifactorial group: combination of several limitations - no limitation: group without any of the previously mentioned limitations, ns – p>0.05; * - p≤0.05; ** - p≤0.01; *** - p≤0.001; **** - p≤0.0001; BL - Baseline; BB - Betablocker; RASi - Renin Angiotensin System Inhibition; MRA - Mineralocorticoid Receptor Antagonist; SGLT2i - Sodium Glucose Transporter 2 Inhibition.

II.3

Skeletal muscle-selective deletion of iron regulatory proteins increases early mortality and impairs cardiac function after transverse aortic constriction.

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Objective: Iron deficiency (ID) is a frequent comorbidity in heart failure (HF) leading to exercise intolerance and adverse outcomes. We hypothesized that skeletal muscle (SkM) ID worsens cardiac adaptation to hemodynamic stress. We explored the impact of transverse aortic constriction (TAC) in mice with SkM-selective ID induced by targeted-deletion of SkM iron regulatory proteins (IRPs) 1 and 2 on cardiac function and survival.
Model: To selectively induce SkM-ID, we crossed iron-regulatory protein (Irp) 1 and 2-floxed mice (Irp1/2$^{f/f}$) with mice expressing Cre recombinase under the control of the myosin light chain promoter 1. These mice (SkM-Irp1/2-KO) enabled us to investigate the impact of SkM-ID on the heart independent of systemic or cardiac ID. SkM-Irp1/2-KO and Irp1/2$^{f/f}$-control mice were subjected to TAC at the age of 8-12 weeks using a 26G needle. Cardiac function was assessed by pressure-volume (PV) loop catheterization.
Results: Cardiac morphology and function were indistinguishable in SkM-Irp1/2-KO and control mice under baseline conditions. Early mortality after TAC (day 1-3) was increased in SkM-Irp1/2-KO mice. One day after TAC, cardiac contractility (7412±638 vs. 11498±605 mmHg/s, P<0.001), ejection fraction (45.3±3.1% vs. 58±3.5%, P=0.02) and cardiac output (10.4±0.4 vs. 13.6±0.7 mL/min, P=0.001) were reduced in SkM-Irp1/2-KO mice. The number of apoptotic (TUNEL+) cells was increased in the left ventricle (LV) of SkM-Irp1/2-KO (1.3±0.1% vs. 0.6±0.09%, P=0.002) on day 1.
One week after TAC, SkM-Irp1/2-KO mice had developed greater cardiomyocyte hypertrophy (cross sectional area, 112±4% vs. Irp1/2$^{f/f}$, P=0.03) and displayed more interstitial left ventricular fibrosis observed through histology (201±32% vs. Irp1/2$^{f/f}$, P=0.03), protein expression of alpha-smooth muscle actin (1.43±0.09 vs. Irp1/2$^{f/f}$, P=0.001) and gene expression of periostin (2.46±0.5 vs. Irp1/2f/f, P=0.02). Metabolomic screening revealed a significant downregulation of acetylcholine (ACh) in the LV of SkM-Irp1/2-KO mice under basal conditions (29±2% vs. Irp1/2$^{f/f}$, P=0.008) and a further reduction on day 1 after TAC 19.4±0.9% vs. Irp1/2$^{f/f}$, P=0.008). Increased expression of the ACh degrading enzyme, acetylcholinesterase (AChE) in LV after TAC (Gene expression: 238±41% vs. 126±8%, P=0.003, protein expression: 109±6% vs 87±5%, P=0.04, compared to basal Irp1/2$^{f/f}$) may have contributed to the observed low ACh abundance.
Conclusion: We show that SkM-selective Irp1 and 2 inactivation promotes SkM-ID and impairs cardiac adaptation to pressure overload. We identify cardiac ACh deficiency and increased AChE as a potential mechanism for SkM-aggravated cardiac dysfunction in pressure overload.

Data are presented as Mean + SEM

II.4

Preemptive iron supplementation prevents cardiac iron deficiency and adverse remodelling after myocardial infarction

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Category: Basic Science
Introduction: Systemic iron deficiency (ID) is a frequent comorbidity in heart failure (HF). Cardiac ID develops independently from systemic iron status and associated with adverse outcomes in HF.
Purpose: We investigated alterations in cardiac iron homeostasis after HF and the potential of preemptive iron supplementation in preventing cardiac ID and attenuating left ventricular (LV) remodelling.
Methods: Male C57BL/6J mice were subjected to myocardial infarction (MI) by left anterior descending coronary artery ligation. Cardiac iron status was analysed in the remote area of the LV 4, 10, and 24 weeks after surgery. Mice received intravenous ferric carboxymaltose (FCM, 15 mg/kg body weight) or saline injections at 12, 16, and 20 weeks after MI. LV function was analysed at 24 weeks by echocardiography and invasive haemodynamics.
Results: Non-haem iron in the remote myocardium was higher at 4 weeks but lower at 24 weeks after MI, compared to sham-

operated mice (161±15%, P<0.001 at 4 weeks, 84±4%, P<0.01 at 24 weeks vs. sham). Cardiac ID at 24 weeks was associated with reduced expression of iron dependent electron transfer chain (ETC) complex I compared with sham-operated mice (42±9%, P<0.0001 vs. sham). Iron regulatory peptide, hepcidin expression was elevated in the remote myocardium at 4 weeks and declined at 24 weeks (235±99%, P<0.05 at 4 weeks, 17±17%, P<0.01 vs. sham). Hepcidin suppression at 24 weeks was related to abundant expression of membrane-bound ferroportin, the only known iron exporter (191±29%, P<0.001 vs. sham). Notably, such regulation was also observed in LV myocardium from failing human hearts, which displayed lower iron content (53±6%, P<0.0001), reduced hepcidin expression (11±18%, P<0.01) and increased membrane-bound ferroportin (195±31%, P<0.01 vs. non-failing control heart). Intravenous FCM injections preserved cardiac iron content and attenuated LV remodelling by improving ejection fraction (saline vs. FCM injection: 29% vs. 44%, P<0.01) and the expression of ETC complex I (171±13%, P<0.0001), compared with saline injected MI mice.

Conclusion: We demonstrate that dynamic changes in cardiac iron status after MI are associated with local hepcidin suppression, leading to cardiac ID long-term after MI. Preemptive iron supplementation maintained cardiac iron content and attenuated adverse remodelling after MI. Our results identify the spontaneous development of cardiac ID as a novel disease mechanism and therapeutic target in postinfarction LV remodelling and HF.

II.5
Hypophosphatemia in HFrEF patients after iron supplementation – ferric carboxymaltose vs ferric derisomaltose

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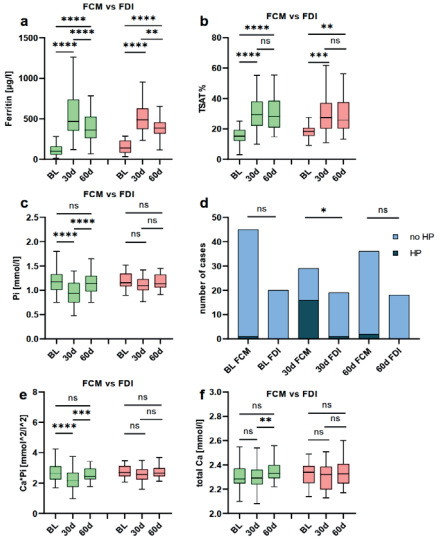
Background: Iron deficiency (ID) is common in heart failure (HF) patients. ESC guidelines recommend intravenous (iv) iron supplementation with ferric carboxymaltose (FCM). Yet recent studies, especially in non-HF cohorts, show that FCM potentially leads to hypophosphatemia (HP). This may occur due to elevated fibroblast growth factor-23 enhancing renal phosphate elimination. Alternative formulations such as ferric derisomaltose (FDI) may not have this effect, however a direct comparison has not been performed.
Purpose: We aimed to compare the effect of FCM and FDI treatment on inorganic phosphate (Pi) in patients with HF with reduced ejection fraction (HFrEF) and ID.
Methods: 66 stable HFrEF patients were enrolled from our prospective registry in 2023. All patients had ID based on the HFA definition. They were prescribed 1000 mg of either FCM (n=46) or FDI (n=20) and underwent follow-up (FUP) evaluations at day 30 and 60 after iv iron supplementation. Iron status, Pi levels and the calcium-phosphate product were recorded and
compared between baseline and FUP and for different iv iron formulations.
Results: The median age of all patients was 69 (IQR 55-75), 53 (80%) of the patients were male, median NT-proBNP was 1785 pg/ml (IQR 540-4824) and median eGFR was 55 ml/min/1.73m^2 (IQR 37-69). There was no significant difference between FCM and FDI patient characteristics. Figure 1 illustrates the results. Both FCM and FDI led to a significant increase in ferritin (p<0.0001) and transferrin saturation (TSAT) (FCM: p<0.0001; FDI: p=0.0003, 0.0011; baseline vs 30d and baseline vs 60d) after 30 and 60 days. Pi decreased significantly in the FCM group after 30 days (p<0.0001), with 16 (36%) cases of real HP (< 0.81 mmol/l), but Pi levels recovered to and were comparable to baseline levels after 60 days (p=ns), with 2 (5%) cases of HP.

The FDI group showed no significant changes in Pi with 1 (5%) case of HP after 30 days. Laboratory HP events were not accompanied by clinical signs of HP in any group. The calcium-phosphate product followed the same pattern as Pi in both groups, while total calcium remained stable compared to baseline.
Conclusions: Both FCM and FDI effectively correct ID. FCM significantly lowers Pi short-term, leading to HP in several cases, whereas FDI produces no such effects. Encouragingly, HP tends to self-correct within 60 days after FCM treatment. Nevertheless, further research is essential to assess the clinical implications of FCM-related HP in patients with HFrEF.



II.6
Iron Deficiency is Associated with Higher Fibroblast Growth Factor 23 Levels in Patients with Chronic Heart Failure: Results from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF)

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Background: Iron deficiency (ID) is highly prevalent and one of the significant prognostic factors in patients with chronic heart failure (HF). Fibroblast growth factor 23 (FGF-23) is a key regulator of phosphate and vitamin D homeostasis, derived from bone and bone marrow. Meanwhile, it has recently been reported that FGF-23 is associated with iron metabolism and

the pathogenesis of heart failure (HF), particularly its severity and adverse outcomes. However, the relationship between ID and FGF-23 levels in HF with reduced ejection fraction (HFrEF) patients remains unclear.
Aim: This study aimed to investigate the association between ID and FGF-23 levels in the HFrEF cohort.
Methods: A total of 240 patients (67±11 years, 80% men) with HFrEF were evaluated for iron metabolism and FGF-23 levels from the Studies Investigating Co-morbidities Aggravating HF (SICA-HF). ID was defined as either a serum ferritin concentration <100 ng/mL or 100-299 ng/mL with transferrin saturation (TSAT) <20%. The Full-length intact FGF-23 level in the serum samples was detected using Human FGF-23 Enzyme Linked-Immuno-Sorbent Assay Kit (Merck KGaA, Darmstadt, Germany). Patients were divided into lower and higher FGF-23 groups based on the median value of 96 pg/mL.
Results: ID was present in 113 (47%) patients. Patients with ID had higher New York Heart Association class, higher prevalence of sarcopenia, higher levels of 25[OH]-vitamin D_3 (18 [13-24] *vs.* 15 [11-21] µg/L, p=0.03) and FGF-23 (131 [80-245] vs. 78 [57-118] pg/mL, p<0.0001), and lower levels of haemoglobin (13.1 [12.4-14.0] *vs.* 13.9 [13.1-14.7] g/dL, p<0.0001) and hepcidin (8 [5-16] vs. 14 [10-26] ng/mL, p<0.0001) than those without ID. Muscle strength and functional capacity were significantly lower in ID patients than in those without (handgrip strength: 36±11 *vs.* 41±12 kg, p=0.0008; quadriceps strength: 37±12 *vs.* 43±13 kg, p=0.0005; peak VO_2: 16.0 ± 4.8 *vs.* 17.9 ± 4.5 ml/min/kg, p=0.004). FGF-23 was positively correlated with high-sensitivity CRP (r=0.23, p=0.001), transferrin (r=0.25, p<0.0001), N-terminal pro-B-type natriuretic peptide (r=0.47, p<0.0001), and end-diastolic posterior wall thickness (r=0.21, p=0.001), and negatively correlated with estimated glomerular filtration rate (r=-0.46, p<0.0001), ferritin (r=-0.27, p<0.0001), TSAT (r=-0.34, p<0.0001), hepcidin (r=-0.30, p=0.0005), haemoglobin (r=-0.15, p=0.02), left ventricular ejection fraction (r=-0.24, p=0.0002), handgrip strength (r=-0.23, p=0.0006), quadriceps strength (r=-0.26, p<0.0001), and peakVO_2 (r=-0.42, p<0.0001). Multivariate logistic regression analysis revealed that ID was significantly associated with higher FGF-23 levels (adjusted OR 5.57, 95% CI 2.12-14.60 p=0.0005).
Conclusions: In patients with chronic stable HFrEF, ID is significantly associated with higher FGF-23 levels.

II.7
Novel biomarkers as possible prognostic tools in the determination of muscle wasting in HF patients.

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Background: Muscle wasting is a comorbidity gaining attention among heart failure (HF) patients and older adults. According to the European Society of Cardiology, its prevalence in HF ranges from 20 to 50%. Identification of sarcopenia in the clinical practice can be challenging, firstly due to its multiple definitions in literature, secondly because of the lack of specific biomarkers that allow early recognition of deterioration of muscle mass. The present study therefore aimed to find possible biomarkers for early screening of muscle wasting.
Methods: Using ProcartaPlex Multiplex Immunoassay (ThermoFisher Scientific, Germany) 43 biomarkers were measured in 169 HF patients from the Studies Investigating Comorbidities Aggravating Heart Failure (SICA-HF). Body composition was assessed by dual energy X-ray absorptiometry. Sarcopenia was defined as a low appendicular lean mass adjusted by height squared (≤7.26 kg/m^2 in men, ≤5.5 kg/m^2 in women).
Results: Patients with sarcopenia (21.3%) were all male, older (72.35±9 *vs.* 66.5±11 years, p=0.006) and presented with lower weight and body mass index (77.31±14 *vs.* 89.82±16 kg, 24.64 [22.18-26.79] *vs.* 29.11 [26-32.71] kg/m^2; both p<0.001), had more frequently ischaemic aetiology (77.8 *vs.* 57.3%, p=0.025) and higher prevalence of iron deficiency (72 *vs.* 36%, p<0.001) and anaemia (44 vs 23%, p=0.009) compared to patients without sarcopenia. Estimated glomerular filtration rate (65.61 [48.6-80.6] *vs.* 71.6[54.9-82.6] mL/min/1.73m^2, p=0.226) showed no difference between the groups. In sarcopenic patients concentrations of periostin (41.06 [32.92-47.89] *vs.* 33.21 [28.39-40.77] pg/mL, p=0.013), vascular endothelial growth factor-a (VEGF-a) (167.72 [84.89-238.21] *vs.* 110.36 [60.33-160.44] pg/mL, p=0.014) and tumor necrosis factor receptor 2 (TNF-R2) (58.93 [44.76-76.56] *vs.* 48.89 [40-63.86], p=0.027) were elevated in comparison to non-sarcopenic patients. Previously suggested biomarkers for sarcopenia, namely osteocalcin (18.6 [12.2-22.2] *vs.* 13.6 [9.83-18] µg/L, p=0.002), osteoprotegerin (5.88 [4.14-7.64] *vs.* 4.52 [3.64-6.08] pmol/L, p=0.016), parathyroid hormone (59.85 [34.5-91.8] *vs.* 42.1 [32.05-64.35] pg/mL, p=0.038) and fibroblast growth factor 23 (153.68 [78.74-819.32] *vs.* 82.9 [56.96-148.72] pg/mL, p=0.002) were higher in sarcopenic patients. Using univariate logistic regression models, VEGF-a (OR 3.51, 95% CI [1.19-10.31], p=0.023) and TNF-R2 (OR 1.02, 95% CI [1.002-1.036], p=0.029) were associated with sarcopenia. In a multivariate logistic regression model, VEGF-a remained an independent predictor of sarcopenia (adjusted OR 4.56, 95% CI [1.03-20.19], p=0.046).
Conclusions: VEGF-a showed a strong association with sarcopenia in HF patients. It is known that VEGF-a plays a role in angiogenesis but further investigation regarding its relation with muscle deterioration and heart failure is needed.

II.8
Body mass-related epigenetic and transcriptional reprogramming in heart failure phenotypes

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Background: Heart failure (HF) is a condition associated with poor prognosis and quality of life. A central risk factor for the development of HF is obesity. The impact of obesity in HF with reduced (HFrEF) and preserved ejection fraction (HFpEF) is still poorly understood.
Aim: This analysis aimed to understand how body mass affects the development and progression of HF and its subtypes. By examining DNA methylation and gene expression changes, molecular alterations related to body mass and their associations with the clinical profile were investigated. In addition, the contribution of genetic risk of obesity was investigated.
Methods: Multi-omics analysis (microarray-based genotyping, beadchip-based DNA methylation, and whole blood RNA sequencing) was performed in the MyoVasc study (N=3,289). To explore the involvement of genetic predisposition, a

polygenic risk score for BMI (BMI_{PRS}) was created. An age, sex and cell type distribution-adjusted epigenome-wide association study (EWAS) identified BMI-related differentially methylated positions in the whole genome. Elastic net regression was performed on
FDR-significant CpG sites to generate a one-dimensional score ($BMI_{CpGscore}$) for use in subsequent analyses. Linear regression was used to elucidate the association between the $BMI_{CpGscore}$ and gene expression. FDR-significant differentially expressed genes (DEGs) were converted to HFpEF- and HFrEF-specific scores by principal component analysis. The relationship between DEG scores and clinical features including cardiac function and structure, vascular function and structure and protein biomarkers was investigated by linear regression.
Results: The BMI_{PRS} accounted for 3% of the variance in BMI. No differences were observed in genetic predisposition between HF phenotypes (p = 0.59). The BMI-EWAS (n_{REF}=525, n_{PEF}=477, $n_{control}$ =702; $n_{CpG\ sites}$= 789,712) identified 1,429 FDR-significant BMI-CpGs. The $BMI_{CpGscore}$ explained 56% of the variance in BMI. The $BMI_{CpGscore}$ was not significantly differently distributed between HF phenotypes, but it was significantly elevated relative to controls in both HFrEF($p=2.7\times10^{-14}$) and HFpEF($p<2.22\times10^{-16}$). A total of 1,829 FDR - significant $BMI_{CpGscore}$-related DEGs were identified in HFrEF individuals, whereas 4,817 FDR significant DEGs were identified in HFpEF individuals. 1,359 DEGs were shared between both phenotypes. HFrEF DEGs showed enrichment for vascular diseases, whereas for HFpEF DEGs were enriched for fatty liver disease, lymphocyte activation. The phenotype-specific DEG scores were associated with distinct clinical features.
Conclusion: Body mass-related epigenetic changes differentially affect gene expression according to HF phenotype. Accordingly, body mass-related epigenetic reprogramming of the transcriptome is linked to distinct clinical features depending on phenotype. The genetic risk of obesity did not differ between HF phenotypes.

II.9
Pericyte and smooth muscle specific knock-out of CXCL12 and its influence on cardiac function after myocardial ischemia in mice

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Introduction: Myocardial infarction (MI), often leads to the development of ischemic heart failure (1). The C-X-C motif chemokine ligand 12 (CXCL12) and the receptor CXCR4 are known to support cardiac repair and play an important role in cardiovascular development (2). However, to date, little is known about cell and tissue specific mechanisms of CXCL12, hindering development of specific therapeutic options. Therefore, we examined the role of smooth muscle cell (SMC) and pericyte-specific CXCL12 action after MI closer.
Methods: We generated two mouse models using smooth muscle protein 22-alpha-Cre and pericyte protein NG2-Cre to specifically ablate CXCL12 in SMCs (SM22-Cre x $CXCL12^{flox/flox}$) and in pericytes (NG2-Cre x $CXCL12^{flox/flox}$). Genotypic verification was achieved through PCR analysis of ear hole biopsies. We conducted a morphological assessment using histological techniques and immunofluorescence staining. Echocardiography was employed to evaluate the dimensions of
cardiac cavities, walls, and overall cardiac function. After inducing myocardial infarction, we continued to monitor cardiac function by echocardiography for an additional 28 days post-MI.
Results: We found that CXCL12 is highly expressed in $SM22^{+}$ smooth muscle cells and in cells surrounding arterial blood vessels by immunofluorescence staining (3). We could not find any inconspicuous behavior, developmental defects, or increased mortality in NG2-$CXCL12^{-/-}$ mice, neither did we find a major co-expression of NG2 and CXCL12 in immunofluorescence. NG2-Cre x $CXCL12^{flox/flox}$ mice without infarction showed normal ventricular geometry and no changes in cardiac function compared to controls. After induction of myocardial infarction, we could observe a reduced ejection fraction (EF) (29.0%±9.7 vs. 40.0%±8.1; n=10; p=0.027) and stroke volume (SV)(19.0µl±3.3 vs. 32.7µl±10.3; n=10; p=0.002) in SM22-Cre x $CXCL12^{flox/flox}$ mice compared to non-transgenic controls, while NG2-Cre x $CXCL12^{flox/flox}$ mice did not show significant changes in EF (34.6%±11.4 vs. 40.0%±8.1; n=10; p=0.368) or SV (27.7µl±7.3 vs. 32.7µl±10.3; n=10; p=0.303).
Conclusion: Our findings indicate that pericyte-specific CXCL12 does not significantly influence cardiac development or its function post-MI. Conversely, the knockout of CXCL12 in SMCs appears to be pivotal for maintaining cardiac function following ischemic events.

II.10
Refinement of cardiac repair after myocardial infarction in mice: Impact of HIF-1α upregulation due to prolyl-hydroxylase inhibition with roxadustat

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Introduction: CXCL12/CXCR4-axis activation is recognized for its role in myocardial repair, primarily by recruiting $CXCR4^{+}$ progenitor cells. This recruitment is facilitated by ischemia-induced activation of hypoxia-inducible factor-1α (HIF-1α) triggering CXCL12. To extend the upregulation of CXCL12 timewise, our objective was to stabilize HIF-1α utilizing roxadustat. Notably, roxadustat is the sole prolyl hydroxylase inhibitor (PHI) that has received clinical approval from the EMA. Our aim with this approach is to ameliorate myocardial remodeling and boost left ventricular (LV) function after myocardial infarction (MI).
Methods: In an in-vitro setting, we assessed the expression of CXCL12 and CXCR4 in human umbilical vascular endothelial cells (HUVEC) post-administration of roxadustat (FG-4592), ranging from 20µM - 1000µM, across various time intervals (1 - 24 hrs). After in-vivo dose-finding experiments, myocardial infarction was induced in BL6/J mice aged 8-10 weeks via LAD-ligation. To investigate the in-vivo effects of HIF-1α-driven CXCL12 upregulation, we administered optimal doses (50mg/kg i.p.) of the PHI roxadustat every 72 hours. Two groups (n=10 each) underwent treatment with either roxadustat or saline over a 28-day period, followed by echocardiographic assessment of cardiac function and histological evaluation. An additional two groups, each comprising 5 mice, received either roxadustat or saline treatment for 7 days. Subsequent analysis focused on the apoptotic index, determined through automated cell counting in DAPI & Tunel stained sections.
Results: We could see a significant upregulation of HIF-1α after exposure of 50-500 µM roxadustat for 4-24 hours in-vitro (HUVEC) and in-vivo (BL6/J mice). Moreover, in-vitro administration of 500 µM roxadustat enhanced CXCR4 and CXCL12 protein levels. We did not find a significant difference in infarcted area size (19.07%±7.86 vs. 24.14%±12,05; n= 10/8; p = 0.297), as well as LV-wall thickness (788.27µm±240.10 vs. 651.40µm±231.47; n=10/8; p = 0.240) 28 days after MI. But we could detect a lowered apoptotic-index in roxadustat treated animals (3.7%±1.1 vs. 6.3%±2.3; p = 0.071) by automated cell counting within the border zone. Echocardiographic analyses revealed a significantly preserved ejection fraction (EF) (46.1%±6.0 vs. 30.6%±8.8; n=10; p<0.001) as well as reduced diastolic (4.18±0.32 vs. 4.70±0.32; p=0.005) and systolic (3.23±0.31 vs. 3.88±0.46; p<0.002) LV diameters in roxadustat treated mice 28 days after MI compared to saline treated controls.
Conclusion: The clinically approved PHI roxadustat revealed increased expression of HIF-1α associated with upregulation of CXCR4 and CXCL12. Administration of roxadustat after MI revealed attenuated infarct remodeling and functional improvement showing its potential in ischemic heart disease.

II.11
Molecular mechanisms of cardiac natriuretic peptide effect on adrenal aldosterone secretion

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The renin-angiotensin-aldosterone system is a key target of several heart failure therapeutics including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone antagonists. Atrial natriuretic peptide (ANP) via its guanylyl cyclase-A (GC-A) receptor inhibits both cyclic adenosine monophosphate (cAMP) and Angiotensin II (Ang II) induced aldosterone secretion. While it is well established that ANP inhibits cAMP-induced aldosterone by cGMP-dependent activation of phosphodiesterase type 2 (PDE2), the molecular mechanism(s) of ANP effect on AngII-induced aldosterone secretion is still unknown.
To elucidate this important gap of knowledge, we established primary cultured bovine aldosterone-producing zona glomerulosa (ZG) cells and CRISPR/Cas9 knock-out (KO) of PDE2. With this model, we can elucidate PDE2-dependent and PDE2-independent effects of natriuretic peptides on aldosterone secretion to fully understand how they affect the renin-angiotensin-aldosterone system in the context of healthy and failing heart.
ANP effects on forskolin-induced aldosterone and cAMP levels were abrogated in PDE2-KO cells as measured using live cell imaging based on the fluorescent cAMP biosensor. However, ANP could still inhibit Ang II-stimulated aldosterone production. In search for possible molecular mechanisms, we have further assessed the regulation of angiotensin-receptor signaling by ANP/GC-A pathway. Interestingly, we could uncover that it inhibits AngII-induced ß-arrestin translocation to angiotensin receptor which is known to be involved in aldosterone secretion. It is well established that PDE2 levels is highly expressed in adrenal ZG cells of different species including humans. Several gene loss-of-function variants of PDE2A gene have been reported to cause hyperplasia and primary aldosteronism in patients. Thus, in addition to dissecting the fundamental molecular mechanism of ANP-induced inhibition of AngII aldosterone secretion, our work may provide a potential therapeutic target for patients with primary aldosteronism and heart failure.

II.12
Cardiac fibrosis fingerprints and pre-clinical development of therapeutic approaches

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Fibrotic diseases affect more than 100 million people worldwide, with myocardial and pulmonary fibrosis accounting for the majority. Current available pharmacological treatment options only slow down the progressive pathological remodeling of the extracellular matrix leading to detrimental tissue stiffness. However, the lack of suitable fibrosis research models hinders the development of efficient and safe anti-fibrotic drugs. This project focuses on the establishment of advanced cardiac fibrosis model systems to study potential anti-fibrotic therapeutics using ultrathin (300 µm) *ex vivo* 3D living myocardial slices (LMS). The preservation of natural multicellularity allows the study of intra- and intercellular communication. We have miniaturized the *ex vivo* LMS to the size of 4 x 4 mm (miniLMS) and developed real-time video-based monitoring of cardiomyocyte contractility in LMS to ensure higher throughput and more sensitive evaluation than other read-out systems. Next, we aim to establish an acute heart failure model by performing a cryoinjury to induce pro-fibrotic molecular signatures in the uninjured remote area. We simultaneously conducted an *in silico* analysis of human data sets from patients with dilated and ischemic cardiomyopathy to identify potential targets and compounds. Our analysis revealed dysregulation of various cysteine proteases in the calpain and cathepsin families, and compound screening identified aloxistatin as our first candidate for testing. We performed dose-finding experiments to determine the non-cardiotoxic concentration by applying aloxistatin to *ex vivo* LMS. Furthermore, Western blot analysis revealed a decreased abundance of pro-fibrotic extracellular fibronectin-1 after aloxistatin treatment. Therefore, further functional investigations and *ex vivo* experiments are planned to further validate the potential of aloxistatin in the clinical setting of cardiac fibrosis.

II.13
Assessment of cardiotoxicity via organomimetic 2D and 3D models

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Introduction: Adverse drug events, such as cardiotoxicity, are major concerns in drug development and a major reason for drug market withdrawal. Despite animal experiments being still state of the art, they no longer meet the contemporary requirements of research. To counteract this, establishment of new methods in compliance with the 3R principle that enable direct use of human material are needed.
Objectives: Bridging the gap of translational research in cardiac model systems, we established a 2D and a 3D platform for assessment of cardiotoxicity using human iPSC-derived cardiomyocytes (hiPSC-CM) and living myocardial slices (LMS) from human, rodent and porcine cardiac tissue.
Materials & methods: The xCELLigence RTCA Cardio ECR detects the effects on 2D human cardiomyocytes to validate cardiotoxicity in real time. hiPSC-CM were cultured and analyzed for 10 days in 10 µg/ml fibronectin coated xCELLigence RTCA Cardio ECR plates. Viability and contractility (impedance and field potential) were assessed before and after treatment with exemplarily given compounds. 300 µm rat LMS were cultivated in MyoDish systems and treated with exemplary compounds to determine viability and changes in contraction force, pattern and time.
Results: Cell index, beat rate, beating amplitude and beating period were chosen as initial read outs and were calculated using the built-in xCELLigence analysis software. Both, cell density and cultivation time after treatment affect several physiological parameters. In LMS, reduced contractility was shown for 0.03 mM MSDH (o-methyl-serine dodecylamide hydrochloride) after 6 h and 12 h indicating measurable functional impact. In comparison to 0.5 mM TAA (thioacetamide) and 0.012 mM CQD (Chloroquine bis(phosphate)) which did not affect LMS contractility (n = 3, means ± SD, Two-way ANOVA).

Conclusion: The combination of 2D and 3D cardiac models offer a variety of possibilities to predict cardiac risk factors and to create comprehensive models for iPSC-derived/primary cardiomyocytes, disease modeling, co-culture approaches, drug testing, monitoring electrophysiology (e.g. rhythm, conduction, contractility, relaxation time) in 2D and 3D cardiac systems enabling the use of human material for research *in vitro* and *ex vivo*.

II.14

MicroRNA-22 as a potential diagnostic tool in patients with heart failure and sarcopenia: Results from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF) and the Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies (SPRINTT)

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Background: MicroRNA-22-3p (miR-22) targets several muscle function-related genes. Our aim was to investigate the diagnostic value of miR-22 in patients with heart failure (HF) and sarcopenia.
Methods: We assessed miR-22 in a derivation cohort of 176 HF patients from the SICA-HF study and validated its results in a cohort of 61 geriatric patients from the SPRINTT study. In the derivation cohort, sarcopenia was defined as appendicular skeletal muscle mass (ASM) index <7.26 kg/m^2 in males and <5.45 kg/m^2 in females. In the validation cohort, sarcopenia was defined as reduced physical function and low appendicular lean mass (ALM; <19.75 kg in males and <15.02 kg in females) without mobility disability. MiR-22 serum concentrations were measured by miR-specific TaqMan RT-qPCR.
Results: In the derivation cohort, the prevalence of sarcopenia was 15.9%. Compared to those without, patients with sarcopenia were significantly older (74.5 [68.7-80.2] *vs.* 68.4 [60.9-74.8]; p=0.001), had lower BMI (25.1 [22.4-26.8] *vs.* 29.2 [26.0-32.9] kg/m^2; p<0.001), higher NT-proBNP levels (3693.2 [1183.3-5000.0] *vs.* 1066.4 [521.3-2453.6] pg/mL; p<0.001), lower LVEF (16.8 [15.0-20.0] *vs.* 35.0 [30.0-40.0] %; p=0.025), lower handgrip strength (31.1 ± 6.0 *vs.* 37.0 ± 13.0 kg; p=0.016), lower absolute peak oxygen uptake (VO_2) (1181.3 ± 379.5 *vs.* 1593.0 ± 487.0 mL/min; p<0.001) and lower distance in 6-minute walk test (389.0 ± 135.5 *vs.* 466.3 ± 120.0 m; p=0.009). Cycle threshold (CT) value after RT-qPCR analysis showed that HF patients with sarcopenia had significantly higher serum levels of miR-22 (5.2±0.8 *vs.* 5.7±0.9 relative expression level CT-values; p=0.032). Multivariate logistic regression analysis revealed that miR-22 levels were significantly associated with sarcopenia in HF patients, even after adjustment for age, diabetes mellitus, LVEF, NT-proBNP levels, and absolute peak VO_2 values (adjusted OR 0.409, 95% CI 0.193-0.867, p=0.020). In the validation cohort, sarcopenic patients accounted for 54.1% and presented with no significant differences in age, sex, BMI and prevalence of comorbidities. Patients with sarcopenia had a significantly lower gait speed during the 4-meter walk (6.5 [5.4-7.3] *vs.* 5.0 [4.3-5.8] sec; p<0.001) and had a higher total gait speed test score (5.9 [5.0-6.5] *vs.* 4.8 [4.1-5.6] sec; p<0.001). In the multivariate logistic regression analysis, miR-22 remained significant independent predictor of sarcopenia when adjusted for age, BMI, heart rate, and the presence of HF and cancer (adjusted OR 0.359, 95% CI 0.185-0.697, p=0.003).
Conclusion: MiR-22 is independently associated with sarcopenia in HF and elderly populations, suggesting its potential as a novel epigenetic biomarker of skeletal muscle alterations.

II.15

Sex-related differences in heart failure pharmacological treatment: Results from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF)

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Background: Heart failure (HF) is a complex clinical syndrome caused by a dysfunctional cardiac system by raising the natriuretic peptide level or existing pulmonary or systemic congestion. Women represent roughly a quarter of patients with HF with reduced ejection fraction (HFrEF), while they account for over half of those with HF with preserved ejection fraction (HFpEF). Important differences in comorbidities and clinical characteristics exist between women and men with HF. These sex-related differences are also observed in the pharmacokinetics and pharmacodynamics of some recommended medications for the treatment of heart failure. It has been shown that as compared with men, women with HFrEF are less often treated with guideline-recommended HF drugs.
Aim: Our aim was to assess whether females receive less medication than males in heart failure cases and how significant this difference is.
Material and methods: We conducted a retrospective analysis of 189 ambulatory stable patients diagnosed with heart failure with reduced ejection fraction (HFrEF) enrolled in the multinational and multicenter clinical trial, SICA HF study (Studies Investigating Comorbidities Aggravating Heart Failure). A variety of characteristics were extracted from the medical reports including baseline clinical characteristics, exercise capacity, and the recommendation of drugs for different heart failure groups. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 26.0.
Results: Although there were fewer females than males in the study (159 *vs.* 30), there was no significant difference in baseline clinical characteristics between the two groups, indicating similarity. Overall prevalence of sarcopenia was 15.9%. Male HF patients had a higher maximal handgrip strenght (38 [32-48] vs. 22 [19.5-27.5] kg; p<0.001) and a higher maximal quadriceps strength test (40.9 ± 13.2 vs 21.07 ± 6.9; p<0.001). The most significant difference in medication was the proportion of patients who received ACE-I (Angiotensin

Converting Enzyme Inhibitors) (male: 71.70% vs female: 50%, p = 0.019). There was no statistically significant difference in the prescription of the other classes of HF medication between males and females.
Conclusion: Men had a higher prescription rate of ACE-I compared to women. No other sexual-related differences in heart failure treatment were seen.

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