Supplementary appendix

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## Investigational sites

**Table S1** Investigational sites and numbers of enrolled patients

| Institution                                                                 | Country       | Principal investigator            | N= |
|----------------------------------------------------------------------------|---------------|----------------------------------|----|
| Semmelweis Medical University, Budapest                                     | Hungary       | Merkely, Béla                    | 18 |
| Unfallkrankenhaus Berlin                                                    | Germany       | Lenz, Corinna                    | 8  |
| Charite Universitätsklinikum - Campus Benjamin Franklin, Berlin             | Germany       | Roser, Mattias Johannes          | 4  |
| Immanuel Klinikum Bernau - Herzzentrum Brandenburg, Bernau bei Berlin       | Germany       | Butter, Christian                | 2  |
| Universitätssklinikum Würzburg                                             | Germany       | Nordbeck, Peter Johann           | 2  |
| Maria Heimsuchung - Caritas-Klinik Pankow                                  | Germany       | Meyhöfer, Jürgen                 | 1  |
| Herzzentrum Leipzig GmbH, Leipzig                                           | Germany       | Döring, Michael                  | 1  |
| **Total: 7 sites**                                                         | **2 countries**|                                  | **36** |
Supplementary methods

**Cardiopulmonary exercise testing: additional information**

The same cardiopulmonary exercise (CPX) protocol was applied during the baseline visit, 1-month follow-up, and 2-month follow-up. To minimise an impact of circadian and metabolic variations on the intra-individual exercise performance, the patients underwent all three CPX tests at the same time of the day and with the same status of food and fluid intake.

Furthermore, all CPX protocols in German patients were performed at one investigational site by the same investigator (author TT) and with the same equipment:

- Treadmill: Pulsar 3p; h/p/cosmos sports & medical gmbh, Nussdorf-Traunstein, Germany;
- Gas analyser: Quark CPET; COSMED, Rome, Italy.

Likewise, all CPX protocols in Hungarian patients were performed at one site (investigator BM) with the same equipment:

- Treadmill: T-2100 / CardioSoft; GE Healthcare, Chicago, United States
- Gas analyser: Spiro-SP TrueFlow; GE Healthcare, Chicago, United States

Since different software for automatic determination of the ventilatory efficiency (VE/VCO₂) slope and oxygen uptake efficiency slope (OUES) in different CPX systems were likely to produce different results, all slopes were manually calculated by an expert blinded to the pacing mode (author DMC). The definite exercise periods were first determined. Then, for the VE/VCO₂ slope, the differences in minute ventilation (VE) and CO₂ production (VCO₂), the dVE and dVCO₂, respectively, were calculated and the quotient dVE/dVCO₂ was determined. Analogously, for the OUES, the corresponding data coordinate points were from the first O₂ production (VO₂) and VE measurements at the start of the exercise, to the last data points recorded at end-exercise. These coordinate data points were processed in the same way as for the ventilatory efficiency slope.
Other assessments: additional information

This section provides additional information on the assessments made at both follow-ups.

Health-related quality of life

The European Quality of Life 5-Dimensions 5-Level (EQ-5D-5L) questionnaire, also known as EuroQol-5D, was used to assess patients’ quality of life in each mode. The questionnaire consists of two pages: the EuroQol-5D descriptive system and the EuroQol visual analogue scale. In the EuroQol-5D descriptive system, patients indicate their status by selecting level of problems (no, slight, moderate, severe, extreme/unable) they experience in each of the five dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. The five scores are converted into a single EuroQol-5D index ranging from 0 (worst health) to 1 (perfect health). In the EuroQol visual analogue scale, respondents report their perceived health status with a single grade between 0 (the worst possible health status) and 100 (the best possible health status).

Subsequently, the Minnesota Living with Heart Failure Questionnaire (MLHFQ) was administered. This standardised instrument for heart failure patients measures the effect of treatments on key physical, emotional, social, and mental dimensions of quality of life by accounting for symptoms, functional limitations, and psychological distress. Patients indicated on a 6-point (0 to 5) Likert scale how much each of 21 facets had prevented them from living as desired. The total MLHFQ score ranges from 0 (best) to 105 (worst health-related quality of life).

Duke Activity Status Index (DASI)

Type and dose of daily energy expenditure play a major role in modulations of health status. DASI is a self-assessment tool comprising the following 12 questions:

Are you able to

1. Take care of self (e.g., eating, dressing, bathing, using the toilet)?
   - No = 0, Yes = 2.75
2. Walk indoors?
   - No = 0, Yes = 1.75
3. Walk 1–2 blocks on level ground?
   - No = 0, Yes = 2.75
4. Climb a flight of stairs or walk up a hill?
   - No = 0, Yes = 5.5
5. Run a short distance?
   - No = 0, Yes = 8
6. Do light work around the house (e.g., dusting, washing dishes)?
   - No = 0, Yes = 2.7
7. Do moderate work around the house (e.g., vacuuming, sweeping floors, carrying in groceries)?
No = 0, Yes = 3.5

(8) Do heavy work around the house (e.g., scrubbing floors, lifting or moving heavy furniture)?
No = 0, Yes = 8

(9) Do yard work (e.g., raking leaves, weeding, pushing a power mower)?
No = 0, Yes = 4.5

(10) Have sexual relations?
No = 0, Yes = 5.25

(11) Participate in moderate recreational activities (e.g., golf, bowling, dancing, doubles tennis, throwing a baseball or football)?
No = 0, Yes = 6

(12) Participate in strenuous sports (e.g., swimming, singles tennis, football, basketball, skiing)?
No = 0, Yes = 7.5

The higher the DASI score (maximum 58.2), the better the functional status of the patient is. DASI score has been shown to provide independent and incremental prognostic information beyond cardio-renal biomarkers with respect to 5-year mortality in a big cohort of patients with stable heart failure.³

D2-R test of attention (mental stress)

The d2-R test, a cancellation test of attention and concentration, is a neuropsychological measure of selective and sustained attention and visual scanning speed. The d2-R is a revised and newly standardised version of the d2 test.⁴ Using a paper and pencil, participants are asked to cross out any letter "d" with two marks above it or below it. The surrounding distractors are e.g., "d" with one or three marks, "p" with two marks, etc. During the test, patients develop mental stress due to speed (they are under time pressure), accuracy and continuity.⁵ The score is calculated as the number of discovered targets minus number of indicated distractors.

Six-minute walk test

A distance covered during the 6-minute walk test is a simple, first-line measure of functional status (i.e., exercise intolerance or physical disability) in patients with mild-to-moderate heart failure.⁶ Arslan et al. found that 6-minute walk distance is a useful prognostic marker of subsequent cardiac death.⁷ Guazzi et al. later demonstrated that 6-minute walk distance correlates well with established prognostic indicators obtained during CPX, the VE/VCO₂ slope and VO₂max;⁶ however, there was no supportive evidence for its use as a prognostic marker as an alternative to or in conjunction with CPX-derived variables.⁶

In our study, patients were instructed to cover the greatest distance possible during the allotted time of 6 minutes, at a self-determined walking speed, pausing to rest when needed, and using their usual walking aids when necessary. Every minute, the patient was informed about the time that has passed. The walking distance was recorded.
Supplementary results

Tables S2 and S3 depict results for secondary outcome measures not shown in the main paper. There was no significant carry-over effect for any outcome, except for the d2-R mental test ($P=0.043$). Likewise, a marginally significant period effect was observed only for the MLHFQ score ($P=0.026$), DASI ($P=0.031$), and 6-minute walk test ($P=0.011$).

### Table S2 Echocardiographic results and NT-proBNP

| Echo parameters        | DDD-40 mode | DDD-CLS mode | Change in DDD-CLS$^a$ | Total change in DDD-CLS$^{a,b}$ N = 17 |
|------------------------|-------------|--------------|-----------------------|----------------------------------------|
| LVEF – %               |             |              |                       |                                        |
| Group 1 (DDD-40 first)$^c$ | 41 ± 10     | 45 ± 9       | 4 ± 8                 | 0.5 ± 4 (+) (P=0.23)                    |
| Group 2 (DDD-CLS first)$^d$ | 48 ± 8      | 45 ± 4       | -3 ± 8                |                                        |
| Cardiac output – l/min |             |              |                       |                                        |
| Group 1$^c$            | 4.5 ± 1.5$^e$ | 4.3 ± 0.8    | -0.2 ± 1.7$^e$        | 0.0 ± 0.7$^i$ (P=0.98)                |
| Group 2$^d$            | 4.0 ± 1.3    | 4.2 ± 0.9    | 0.2 ± 0.8             |                                        |
| Left atrial volume – ml|             |              |                       |                                        |
| Group 1$^c$            | 78 ± 27     | 76 ± 38      | -2 ± 27               | -6 ± 12 (+) (P=0.30)                   |
| Group 2$^d$            | 69 ± 21     | 58 ± 13      | -11 ± 15              |                                        |
| LVEDV – ml             |             |              |                       |                                        |
| Group 1$^c$            | 172 ± 65    | 170 ± 40     | -2 ± 39               | -4 ± 16 (+) (P=0.81)                   |
| Group 2$^d$            | 136 ± 46    | 130 ± 54     | -5 ± 21               |                                        |
| LVESV – ml             |             |              |                       |                                        |
| Group 1$^c$            | 106 ± 51    | 93 ± 37      | -13 ± 30              | -0.4 ± 16 (+) (P=0.76)                |
| Group 2$^d$            | 71 ± 30     | 83 ± 28      | 12 ± 35               |                                        |
| PAP – mmHg             |             |              |                       |                                        |
| Group 1$^c$            | 24 ± 9$^g$  | 29 ± 8$^h$   | 4 ± 5$^f$             | 3 ± 4$^i$ (-) (P=0.17)                |
| Group 2$^d$            | 36 ± 10     | 38 ± 14      | 2 ± 10                |                                        |
| NT-proBNP – pg/ml      |             |              |                       |                                        |
| Group 1$^c$            | 769 ± 790   | 973 ± 1174   | 205 ± 561             | -1 ± 259 (+) (P=1.00)                 |
| Group 2$^d$            | 808 ± 636   | 602 ± 461    | -206 ± 444            |                                        |

Data are shown as mean ± standard deviation. P-values are reported to 2 significant decimal places.

$^a$ Intra-individual difference between DDD-CLS and DDD-40.

$^b$ Plus or minus in brackets indicate favourable (+) or unfavourable (-) change in the DDD-CLS mode.

$^c$ N=10 if not otherwise stated (patients with full data sets regarding ventilatory efficiency slope).

$^d$ N=7 if not otherwise stated (patients with full data sets regarding ventilatory efficiency slope).

$^e$ N=9 (1 data point missing).

$^f$ N=16 (1 data point missing).

$^g$ N=7 (3 data points missing).

$^h$ N=8 (2 data points missing).

$^i$ N=14 (3 data points missing).

LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PAP, pulmonary artery pressure.
Table S3 Other secondary outcome measures

|                         | DDD-40 mode | DDD-CLS mode | Change in DDD-CLS<sup>a</sup> | Total change in DDD-CLS<sup>a,b</sup> |
|-------------------------|-------------|--------------|-----------------------------|----------------------------------|
| **Health-related QoL**  |             |              |                             | N = 17                           |
| EuroQol-5D index        |             |              |                             |                                  |
| Group 1 (DDD-40 first)<sup>c</sup> | 0.88 ± 0.18 | 0.87 ± 0.20 | -0.01 ± 0.05                | 0.07 ± 0.08 (+) (P=0.28)         |
| Group 2 (DDD-CLS first)<sup>d</sup> | 0.72 ± 0.33 | 0.88 ± 0.17 | 0.16 ± 0.25                 |                                  |
| EuroQol VAS             |             |              |                             |                                  |
| Group 1<sup>c</sup>     | 58.0 ± 23.6 | 63.0 ± 23.2  | 5.0 ± 9.4                   | 1.4 ± 5.3 (+) (P=0.64)           |
| Group 2<sup>d</sup>     | 71.4 ± 15.7 | 69.3 ± 18.4  | -2.1 ± 12.2                 |                                  |
| MLHFQ                   |             |              |                             |                                  |
| Group 1<sup>c</sup>     | 33.1 ± 21.0 | 28.5 ± 20.9  | -4.6 ± 8.9                  | -0.4 ± 3.8 (+) (P=0.62)          |
| Group 2<sup>d</sup>     | 24.6 ± 29.9 | 28.3 ± 30.2  | 3.7 ± 5.1                   |                                  |
| **DASI**                |             |              |                             |                                  |
| Group 1<sup>c</sup>     | 33.9 ± 16.2 | 41.2 ± 14.6  | -4.0 ± 7.7                  | 1.6 ± 5.2 (+) (P=0.58)           |
| Group 2<sup>d</sup>     | 35.1 ± 17.1 | 31.1 ± 15.2  | 3.7 ± 5.1                   |                                  |
| **D2-R mental test**    |             |              |                             |                                  |
| Group 1<sup>c</sup>     | 131.2 ± 45.0| 131.8 ± 40.9| 0.6 ± 10.9                  | -2.7 ± 7.3 (-) (P=0.76)          |
| Group 2<sup>d</sup>     | 93.9 ± 18.2 | 87.9 ± 21.7  | -6.0 ± 18.9                 |                                  |
| **6-min walk distance** |             |              |                             |                                  |
| Group 1<sup>c</sup>     | 359 ± 94<sup>e</sup> | 392 ± 105<sup>e</sup> | 33 ± 25<sup>e</sup> | 10 ± 13<sup>f</sup> (+) |
| Group 2<sup>d</sup>     | 444 ± 152   | 432 ± 136    | -12 ± 28                    |                                  |

Data are shown as mean ± standard deviation. P-values are reported to 2 significant decimal places.

<sup>a</sup>Intra-individual difference between DDD-CLS and DDD-40.
<sup>b</sup>Plus or minus in brackets indicate favourable (+) or unfavourable (-) change in the DDD-CLS mode.
<sup>c</sup>N=10 if not otherwise stated (patients with full data sets regarding ventilatory efficiency slope).
<sup>d</sup>N=7 if not otherwise stated (patients with full data sets regarding ventilatory efficiency slope).
<sup>e</sup>N=9 (1 data point missing).
<sup>f</sup>N=16 (1 data point missing).

DASI, Duke Activity Status Index; MLHFQ, Minnesota Living with Heart Failure Questionnaire; QoL, quality of life; VAS, visual analogue scale.
Supplementary discussion

Criteria for severe chronotropic incompetence

Definitions of chronotropic incompetence (CI) and severe CI are not standardised, and different authors apply different criteria. In our study, severe CI was defined similarly as in previous trials of rate-adaptive cardiac resynchronisation therapy (CRT), in order to have a reference regarding the outcome of CLS. Thus, our criteria for severe CI were a maximum heart rate <75% of the age-predicted maximum heart rate (APMHR = 220-age) or inability to utilise at least 50% of heart rate reserve (%HRR) during bicycle ergometry.

However, the widely used formula 220-age has been determined for healthy population and is probably overestimating the APMHR in heart failure. In our study, patients with severe CI had an average intrinsic peak heart rate during bicycle ergometry of ≈65% of APMHR (corresponding to ≈98 beats/min [bpm]) and a peak %HRR utilisation of ≈37% on average. This low percentage of %HRR utilisation appears more conform with the perception of “severe CI” than 65% of APMHR is, because the presence of any CI is commonly diagnosed with a much higher cut-off value for %HRR utilisation of 80%.

Furthermore, drugs such as beta-blockers (a mainstay in the treatment of systolic heart failure) may attenuate the exercise-induced increase in heart rate, possibly requiring another definition of cut-off values for CI. Moreover, the picture of the effect of beta-blockers on CI is still inconsistent and the effect may depend on the stage of heart failure (less effect in advanced stage). Definition of severe CI remains arbitrary. New studies are needed to define the cut-off values uniformly and optimally so as to increase the benefit of CI assessment and treatment.

Atrial pacing in heart failure

Atrial pacing in heart failure is considered detrimental by some investigators and has been discussed controversially. The atrial stimulation (excitation spreading through atrial muscle) leads to a delay in the activation of the left atrium, which can impair left ventricular filling. Higher heart rates may aggravate the problem.

The BIO|CREATE study, however, relied on the findings of the PEGASUS CRT (Pacing Evaluation-Atrial Support Study in CRT) multicentre, randomised, 3-arm trial. To evaluate the role of atrial support pacing in advanced heart failure patients with a CRT indication, PEGASUS CRT investigators randomised 1433 patients to a DDD-40, DDD-70, or DDDR-40 mode for 1 year. The primary endpoint was a clinical composite score that included all-cause mortality, heart failure events, NYHA functional class, and patient global self-assessment.

Although the rationale of PEGASUS CRT suggested that CRT patients might benefit from atrial support pacing, previous results from the DAVID (Dual Chamber and VVI Implantable Defibrillator) trial showed a tendency toward an increased composite endpoint of heart failure events and death in DDDR-70 versus VVI-40 mode, which was most likely
attributable to the deleterious effects of right ventricular pacing and possibly to atrial
dysynchrony induced by atrial pacing as an additional factor.

In the end, the PEGASUS CRT trial did not demonstrate superiority of atrial support
pacing (DDD-70, DDDR-40) over atrial tracking (DDD-40), but there were no concerns about
its safety, suggesting that rate-adaptive pacing or/and the use of higher basic pacing rates is
reasonably safe when clinically indicated.

**Sensors in CRT devices**

A variety of sensors have been utilised in rate-adaptive pacemakers and implantable
cardiodefibrillators (ICDs), including accelerometer (the oldest and the most widely
used sensor), minute ventilation (metabolic sensor with a slower response than
accelerometer), right ventricular impedance with Closed Loop Stimulation (CLS; investigated
in our study, surrogate for the inotropic state and ventricular contractility), peak endocardial
acceleration, QT interval, and others. Some of these sensors may be in the process of
incorporation into CRT devices, but there is a paucity of published data on their clinical
performance. To our best knowledge, the effectiveness of rate-adaptive sensors other than
accelerometer is generally unknown in the CRT population. In the main paper, we
therefore mention only the accelerometer sensor as an alternative to CLS.

Moreover, BIO|CREATE is the first study to systematically evaluate the treatment effects
of CLS in CRT patients with severe CI. Previously, in the PROVIDE (Protos CLS Validation:
Improvement in Day-to-day Exercise), AVAIL CLS/CRT (AV Node Ablation with CLS and CRT
Pacing Therapies for Treatment of Atrial Fibrillation), and CONFIRM (Closed Loop
Stimulation: Heart Failure Indexing and Rate Modulation) trials, clinical performance of
pacemakers and biventricular devices with CLS sensor appeared appropriate in patients with
heart failure (NYHA class I-III). In these previous randomised trials, CLS was not inferior to
the accelerometer sensor.

Moreover, the PROVIDE investigators compared the CLS rate after the end of a 6-minute
walk test for chronotropically incompetent patients in worse (NYHA II/III) versus better
(NYHA I) physical condition and found that the rate was higher for worse condition (97 ± 18
bpm, vs. 85 ± 16 bpm for better condition; P=0.0012). In contrast, the accelerometer
sensor increased pacing rate similarly in all patients. It was concluded that CLS is adapting
the heart rate according to the demanded cardiac output.

We are not aware if intracardiac impedance changes according to the CLS principle were
compared in patients with and without heart failure. The impedance is continuously
measured during every cardiac cycle, generating a characteristic impedance curve. During
progressive contraction, the impedance curve is changing. The differential area between the
curve under load and the reference curve at rest is translated into a pacing rate. The so-
called Auto Response Factor is an automatic tool to achieve the programmed upper sensor
rate independently from the relative difference of the differential area. Based on this
concept, CLS is designed to work also in heart failure patients with low ventricular
contractility.
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