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ORIGINAL RESEARCH

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Endocrine hormone imbalance in heart failure with reduced ejection fraction: A cross-sectional study

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Abstract

Background and Aims: Sustained neurohormonal activation plays a central role in the progression of heart failure (HF). Other endocrine axes may also be affected. It was the aim of this study to examine the endocrine profile (thyroid, parathyroid, glucocorticoid, and sex hormones) in a contemporary sample of patients with HF and reduced ejection fraction (EF) on established disease-modifying therapy.

Methods: This study prospectively measured morning fasting hormones in 52 ambulatory and stable HF patients with EF < 50% on disease-modifying therapy (mean age 63 ± 11 years, 29% female, mean LVEF 32 ± 9.6%) and compared them to 54 patients at elevated risk for HF (61 ± 12 years, 28% female) and 62 healthy controls (HC; 61 ± 13 years, 27% female). Main comparisons were performed using one-way analysis of variance. Associations with biomarkers were studied with linear regression.

Results: HF patients showed a reduced free triiodothyronine (fT3)/free thyroxine (fT4) ratio compared to HC (0.30 ± 0.06 vs. 0.33 ± 0.05, $p = 0.046$). Parathyroid hormone (PTH) and cortisol were increased in HF compared to both HC (median [IQR] 59 [50–84] vs. 46 [37–52] ng/L, $p < 0.001$ and 497 ± 150 vs. 436 ± 108 nmol/L, $p = 0.03$, respectively) and patients at risk (both $p < 0.001$). Total testosterone was reduced in male HF compared to HC (14.4 ± 6.6 vs. 18.6 ± 5.3 nmol/L; $p = 0.01$). No differences in TSH, estradiol, progesterone, and prolactin were found. Lower fT3 levels were found in HF with EF < 40% versus EF 40%–49% (4.6 ± 0.3 vs. 5.2 ± 0.7 pmol/L, $p = 0.009$). In HF patients, fT3 was an independent predictor of NT-proBNP and high-sensitivity troponin T in multiple regression analysis. PTH was positively associated with NT-proBNP.

Conclusion: There is evidence of endocrine hormonal imbalance in HF with reduced EF beyond principal neurohormones and despite the use of disease-modifying therapy.

KEYWORDS
cortisol, heart failure, parathyroid hormone, progesterone, testosterone, thyroid hormones

1 | INTRODUCTION

Heart failure (HF) with reduced ejection fraction (HFrEF) is characterized by neurohormonal activation—activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS) in particular.[1] Beyond these principal neurohormones, patients with HFrEF show substantial alterations in several other endocrine axes.[2] Thyroid hormone is a key regulator of energy metabolism and interest in the concept of metabolic failure as a driver of HF has been renewed recently.[3] In HFrEF, reduced levels of free triiodothyronine (fT3), the active form of thyroid hormone, are common and predict a worse prognosis.[4] Parathyroid hormone (PTH) which has a central role in calcium and phosphate homeostasis, correlates with disease severity and predicts outcomes in HF.[5] Imbalance of anabolic and catabolic hormones has also been described in HFrEF, including elevated cortisol[6] and reduced testosterone.[7] Female sex hormones may also be involved in HF pathogenesis. For example, both low and high estradiol levels were associated with mortality in male HFrEF patients.[8] The pituitary hormone prolactin, which is closely related to estrogen metabolism and increases in response to stress, has also been found to predict mortality and rehospitalizations in HF.[9]

Most of the studies on endocrine hormones in HF were performed in the 1990s to early 2000s measuring only selected hormones in patients with varying degrees of disease-modifying therapy and clinical stability. Our aim was to measure the endocrine hormonal profile in a more contemporary cohort of stable and ambulatory patients with HF and reduced left-ventricular ejection fraction (LVEF < 50%) on established disease-modifying therapy.

2 | MATERIAL AND METHODS

2.1 | Study design and protocol

This was an observational single-center study prospectively investigating the role of endocrine hormones in HF patients with a left ventricular ejection fraction <50% compared to controls. The study protocol was approved by the local ethics committee (BASEC No. PB_2016-01517) and conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki. All participants provided written informed consent. Participants were included in the study if they fulfilled one of the following criteria: (1) Patients with a diagnosis of chronic HF according to the 2012 European Society of Cardiology guidelines in compensated clinical status, ambulatory and on established disease-modifying therapies with an LVEF of <50% (HF group), (2) Controls at elevated risk for heart failure, defined by either the presence of coronary artery disease or at least one major cardiovascular risk factor (hypertension, dyslipidemia, diabetes) but without any known diagnosis, symptoms, or signs of heart failure and no LVEF of <50% (risk group), (3) Healthy controls as defined by nonsmoking volunteers, aged 35 years and older, without any known cardiovascular risk factor or any symptomatic or known cardiovascular disease (HC group). The exclusion criteria of the study were primary manifest hypothyroidism or hyperthyroidism, other primary endocrinopathies, amiodarone therapy, any hormonal supplementation (including thyroid replacement therapy, corticosteroid therapy, testosterone replacement therapy, oral contraceptives, or menopausal hormone therapy), and nonmenopausal women.

After signing informed consent, participants were invited to the main study visit for obtaining clinical parameters and phlebotomy. All participants were instructed to remain fasted for at least 8 h (except water), refrain from coffee, alcohol, or cigarette consumption for at least 12 h, avoid unusual exercise the day before the examination, and only present in a stable medical state (especially free of infections or acute illnesses).

2.2 | Laboratory assessments

Blood samples were obtained in the fasted state using heparin plasma and serum vials in the morning at the beginning of the study visit. The samples were analyzed on the same day at the Institute of Clinical Chemistry, University Hospital Zurich using standard clinical routine methods. Thyroid-stimulating hormone (TSH), fT3, free thyroxine (fT4), prolactin, estradiol, progesterone, total testosterone, PTH, basal serum cortisol, high-sensitivity cardiac troponin T (hs-troponin T), and N-terminal pro-brain natriuretic peptide (NT-proBNP) were analyzed with electrochemiluminescence immunoassays (ECLIA) using the COBAS 8000 autoanalyzer (e 801 module) by Roche diagnostics (Mannheim). Undetectable values were replaced by half the lower limit of detection.[10]

2.3 | Statistical analysis

Statistical analysis was performed with JMP 14.3 (SAS Institute). Figures were prepared with GraphPad Prism 9.0 (GraphPad Software). The main outcome parameters and baseline parameters were tested with one-way analysis of variance for parametric and Wilcoxon or Kruskal–Wallis test for nonparametric variables. Comparisons of more than two groups were adjusted for multiple comparisons using the Tukey–Kramer post hoc test for parametric data and the Dunn's test for nonparametric data with comparison between all groups. Categorical variables were tested with the χ^2 test or Fisher's exact test as appropriate. Correlations were assessed with simple linear regression with Pearson correlation coefficients for parametric data, and Spearman correlation for nonparametric data. Multiple linear regression analysis was performed to study the relationship of endocrine hormones with cardiac biomarkers NT-proBNP and hs-troponin T and potential confounding variables. Based on known associations,[11] age, body mass index (BMI), estimated glomerular filtration fraction (eGFR), and LVEF were included in the model. All tests were two-sided and a $p < 0.05$ was considered significant.

3 | RESULTS

3.1 | Baseline characteristics

After screening, 7 participants were excluded due to amiodarone intake, 13 participants due to thyroid hormone intake, 4 participants due to manifest primary hypothyroidism, 1 participant due to manifest hyperthyroidism, and 11 participants due to intake of other hormones. The final study sample included 62 eligible healthy controls (*HC group*), 54 patients at elevated risk of heart failure (*risk group*), and 52 patients with HF and LVEF < 50% (*HF group*). The baseline characteristics of the final study population are shown in Table 1. Age and sex were comparable between HF patients (mean age 63.2 ± 10.9 years, 29% female), patients at risk (mean age 60.9 ± 12.4 years, 28% female), and HC (61.1 ± 13.4 years, 27% female). HF patients had higher BMI (28.4 ± 5.6 kg/m^2) than HC (24.7 ± 3.3 kg/m^2, $p < 0.001$).

HF patients had a mean LVEF of 32 ± 9.6%, significantly elevated levels of NT-proBNP and hs-troponin T, and reduced renal function compared to both control groups ($p < 0.001$ respectively). The etiology of HF was ischemic cardiomyopathy ($n = 27$), idiopathic dilated cardiomyopathy (DCM, $n = 18$), valvular cardiomyopathy ($n = 6$) and noncompaction cardiomyopathy ($n = 1$). The majority of patients were in New York Heart Association (NYHA) symptom class II (class I $n = 8$, class II $n = 34$; class III $n = 10$).

Most comorbidities (hypertension, dyslipidemia, smoking, and CAD) were not significantly different between HF and risk group patients with the exception of diabetes mellitus (HF 38% vs. risk group 19%, $p = 0.02$). Differences in laboratory parameters and drug therapy are shown in Table 1. The majority of patients with HF were on disease-modifying therapy with ACE inhibitors or angiotensin receptor blockers (92% of patients) and beta-blockers (92% of patients). MRAs were taken by 63% of HF patients and 75% of patients were under loop diuretics.

Baseline parameters of patients with HFrEF (LVEF < 40%, $n = 38$) compared with HFmrEF (LVEF 40%–49%, $n = 14$) and HC are shown in Supporting Information: Table S1. No significant differences in age, sex, vital parameters, comorbidities, and most laboratory parameters were observed between HFrEF and HFmrEF patients. Notable differences were higher NT-proBNP and hs-troponin T in HFrEF compared to HFmrEF. More patients in the HFrEF group were on MRA (76%) compared to HFmrEF patients (29%; $p = 0.003$).

3.2 | Thyroid hormones axis

Hormone measurements are shown in Table 2. There were no significant differences in TSH, fT3, and fT4 between HF patients and controls (Figure 1A–C). The fT3/fT4 ratio was significantly lower in HF patients (0.30 ± 0.06) than in HC (0.33 ± 0.05, $p = 0.03$, Figure 1D).

Thyroid hormones according to the EF subgroup (LVEF < 40% vs LVEF 40%–49%) are shown in Supporting Information: Figure S1. HFrEF patients had significantly lower fT3 (4.6 ± 0.3 pmol/L) than HFmrEF patients (5.2 ± 0.7 pmol/L, $p = 0.009$) and HC (4.8 ± 0.4, $p = 0.04$). Likewise, the fT3/fT4 ratio was significantly lower in HFrEF patients compared to HFmrEF and HC ($p = 0.049$ and $p = 0.004$, respectively). A lower fT3/fT4 ratio was found in HF patients with NYHA class III compared to class II (Supporting Information: Figure S2D).

In HF patients, fT3 correlated inversely with the cardiac biomarkers log(NT-proBNP) ($r^2 = 0.35$, $p < 0.001$, Figure 2A) and log(hs-troponin T) ($r^2 = 0.37$, $p < 0.001$ and Figure 2B; nonlogarithmic results, Supporting Information: Figure S3A and B). LVEF correlated positively with fT3 levels in HF patients ($r^2 = 0.22$, $p < 0.001$, Figure 2C). fT3 remained an independent predictor of log(NT-proBNP) and log(hs-troponin T) in multiple linear regression including age, renal function, BMI, and LVEF in HF patients (Supporting Information: Table S2). fT3 was also independently associated with LVEF in multiple regression analysis including age, renal function, BMI, and log(NT-proBNP) (Supporting Information: Table S3). When looking at potential confounders, only log(NT-proBNP) and BMI significantly predicted levels of fT3 in multiple regression analysis, but not age, sex, smoking status, LDL cholesterol, diabetes mellitus, estimated GFR, treatment with ACE-inhibitors or ARBs, beta-blockers or mineralocorticoid antagonists (Supporting Information: Table S4).

3.3 | PTH

Logarithmized PTH was higher in HF patients compared to patients at risk and HC (both $p < 0.001$; Table 2 and Figure 3A; nonlogarithmic results are shown in Supporting Information: Figure S3C). There were no significant differences in log(PTH) between HFrEF and HFmrEF (Supporting Information: Figure S1E), No significant differences in log (PTH) were found between HF patients with versus without MRA therapy, diabetes mellitus or CAD (data not shown). HF patients on loop diuretics had significantly higher PTH than patients without ($p = 0.049$ for logarithmized PTH, Figure 3B, nonlogarithmic results shown in Supporting Information: Figure S3D). Higher PTH was found in HF patients with NYHA class III compared to II and I (Supporting Information: Figure S2E).

Log(PTH) correlated weakly with log(NT-proBNP) ($r^2 = 0.16$, $p = 0.003$, Supporting Information: Figure S4A). No significant correlations with log(hs-troponin T) or LVEF were found (Supporting Information: Figures S4B–C). In multiple regression analysis including age, BMI, LVEF, and renal function, log(PTH) remained an independent predictor of log(NT-proBNP) (Supporting Information: Table S5). Age, estimated GFR, and log(NT-proBNP) predicted levels of log(PTH), but not sex, BMI, smoking, LDL cholesterol, diabetes mellitus, treatment with ACE inhibitors or ARB, beta-blockers, or MRA (Supporting Information: Table S4).

3.4 | Cortisol

Fasting morning plasma cortisol was significantly higher in HF patients compared to both risk patients and HC ($p < 0.001$ and

TABLE 1 Baseline characteristics

Parameter	Healthy controls ($n = 62$)	Elevated risk for HF ($n = 54$)	Heart failure ($n = 52$)	p Value HC versus HF	p Value Risk versus HF
Clinical characteristics					
Age (years)	61.1 ± 13.4	60.9 ± 12.4	63.2 ± 10.9	0.64	0.62
Female sex (%)	17 (27%)	15 (28%)	15 (29%)	0.87	0.91
BMI (kg/m^2)	24.7 ± 3.3	27.3 ± 4.1	28.4 ± 5.6	**<0.001**	0.36
Systolic BP (mmHg)	126 ± 11	135 ± 18	120 ± 22	0.16	**<0.001**
Diastolic BP (mmHg)	78 ± 9	82 ± 11	71 ± 12	**0.003**	**<0.001**
Heart rate (beats/min)	65 ± 11	66 ± 10	66 ± 11	0.80	1.0
Body temperature (°C)	36.6 ± 0.3	36.5 ± 0.3	36.5 ± 0.3	0.43	0.99
LVEF (%)[a]	ND	58 ± 8	32 ± 9.6	-	**<0.001**
Comorbidities					
Hypertension (%)	0 (0%)	25 (46%)	30 (58%)	**<0.001**	0.24
Dyslipidemia (%)	0 (0%)	32 (59%)	31 (60%)	**<0.001**	0.97
Diabetes mellitus (%)	0 (0%)	10 (19%)	20 (38%)	**<0.001**	**0.02**
Current smoking (%)	0 (0%)	19 (35%)	12 (23%)	**<0.001**	0.17
Coronary artery disease (%)	0 (0%)	26 (48%)	32 (62%)	**<0.001**	0.17
Laboratory parameters					
Hemoglobin (g/L)	147.6 ± 10.6	146.4 ± 12.8	137.6 ± 14.4	**<0.001**	**0.002**
Leukocytes (G/L)	5.1 ± 0.9	6.2 ± 1.8	6.9 ± 1.6	**<0.001**	0.07
Sodium (mmol/L)	141.2 ± 1.5	140.3 ± 2.3	139.1 ± 2.6	**<0.001**	**0.02**
Potassium (mmol/L)	4.0 ± 0.3	4.0 ± 0.3	4.2 ± 0.4	**0.006**	**0.04**
Calcium, total (mmol/L)	2.3 ± 0.1	2.4 ± 0.1	2.4 ± 0.1	**0.003**	0.98
Phosphate (mmol/L)	0.9 ± 0.1	0.9 ± 0.2	1.1 ± 0.2	**<0.001**	**<0.001**
Total cholesterol (mmol/L)	5.2 ± 0.6	5.3 ± 1.4	4.8 ± 1.5	0.10	0.05
LDL cholesterol (mmol/L)[b]	3.1 ± 0.5	3.2 ± 1.3	2.6 ± 1.1	**0.03**	**0.01**
HDL cholesterol (mmol/L)	1.7 ± 0.4	1.4 ± 0.5	1.2 ± 0.4	**<0.001**	0.08
Triglycerides (mmol/L)	1.0 ± 0.4	1.6 ± 1.0	2.1 ± 1.9	**<0.001**	0.16
Fasting plasma glucose (mmol/L)	5.3 ± 0.4	5.8 ± 1.2	6.9 ± 2.4	**<0.001**	**0.002**
Fasting plasma lactate (mmol/L)[c]	1.2 ± 0.3	1.2 ± 0.4	1.5 ± 0.4	**<0.001**	**0.005**
hs-CRP (mg/L) [Median (IQR)]	0.9 (0.5–1.8)	1.1 (0.6–2.0)	2.2 (1.2–4.9)	**<0.001**[d]	**0.002**[d]
eGFR CKD-EPI (ml/min/1.73 m^2)	86.1 ± 17.9	83.5 ± 19.5	64.1 ± 18.9	**<0.001**	**<0.001**
NT-proBNP (ng/L) (Median [IQR])	58 (43–108)	86 (33–150)	805 (371–1640)	**<0.001**[d]	**<0.001**[d]
hs-Troponin T (ng/L) [Median (IQR)]	5 (3–8)	6 (3-9)	14 (8–28)	**<0.001**[d]	**<0.001**[d]
Concomitant therapies					
ACE inhibitor/ARB (%)	0 (0%)	26 (48%)	48 (92%)	**<0.001**	**<0.001**
Beta blocker (%)	0 (0%)	20 (37%)	48 (92%)	**<0.001**	**<0.001**
Mineralocorticoid antagonist (%)	0 (0%)	2 (4%)	33 (63%)	**<0.001**	**<0.001**
Loop diuretic (%)	0 (0%)	2 (4%)	39 (75%)	**<0.001**	**<0.001**
Thiazide diuretic (%)	0 (0%)	9 (17%)	7 (13%)	**0.003**	0.64
Calcium channel blocker (%)	0 (0%)	5 (9%)	6 (12%)	**0.008**	0.70

TABLE 1 (Continued)

Parameter	Healthy controls ($n = 62$)	Elevated risk for HF ($n = 54$)	Heart failure ($n = 52$)	p Value HC versus HF	p Value Risk versus HF
Aspirin (%)	3 (5%)	31 (57%)	31 (60%)	**<0.001**	0.81
Anticoagulant (%)	0 (0%)	4 (7%)	16 (31%)	**<0.001**	**0.002**
Statin (%)	0 (0%)	25 (46%)	35 (67%)	**<0.001**	**0.03**
Amiodarone (%)	0 (0%)	0 (0%)	0 (0%)	-	-
Vitamin/mineral supplement (%)	17 (27%)	8 (15%)	9 (17%)	0.20	0.72
Non-insulin antidiabetic drugs (%)	0 (0%)	7 (13%)	13 (25%)	**<0.001**	0.11
SGLT2-inhibitor (%)	0 (0%)	0 (0%)	2 (4%)	0.24	0.21
Insulin therapy (%)	0 (0%)	2 (4%)	8 (15%)	**0.001**	0.05
ICD (%)	0 (0%)	0 (0%)	26 (50%)	**<0.001**	**<0.001**
CRT (%)	0 (0%)	0 (0%)	14 (27%)	**<0.001**	**<0.001**

Note: Mean values ± standard deviation are shown unless otherwise specified. Bold values denote significant results. P-values after adjustment for multiple comparisons are shown for all continuous variables.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CRP, C-reactive protein; CRT, cardiac resynchronization therapy; eGFR CKD-EPI, estimated glomerular filtration rate as calculated by chronic kidney disease epidemiology collaboration formula; HC, healthy controls; HDL, high-density lipoprotein; HF, heart failure; hs, high sensitivity; ICD, implantable cardioverter-defibrillator; IQR, interquartile range (25%–75%); LDL, low-density protein; NT-proBNP, N-terminal pro-brain natriuretic peptide; SGLT, sodium-glucose linked transporter.

[a]LVEF was measured in all HF patients, but was only available in 23 patients at elevated risk for HF. No echocardiograms were performed in HC.

[b]Lactate was not measured in one HC, four risk for HF, and six HF participants due to technical reasons.

[c]Statistical analysis performed using logarithmic data.

[d]LDL cholesterol was not measured in four HF patients due to elevated triglycerides.

$p = 0.03$, respectively, Table 2 and Figure 3C). No significant differences in cortisol were found between HFmrEF and HFrEF (Supporting Information: Figure S1F). Higher cortisol levels were found in HF patients with NYHA class III compared to II (Supporting Information: Figure S2F). No differences in cortisol between HF patients with BMI below or at and above the median were observed (Figure 3D). Also, no significant difference in cortisol was found between HF patients on spironolactone as compared to those without ($p = 0.38$).

No correlation between cortisol and log(NT-proBNP) or LVEF was found in HF patients (Supporting Information: Figure S4D and F). There was a weak positive association of cortisol with hs-troponin T ($r = 0.36$, $r^2 = 0.13$, $p = 0.008$, Supporting Information: Figure S4E). Higher cortisol levels were independently associated with lower BMI and lower estimated eGFR after multiple regression including age, sex, smoking, LDL cholesterol, diabetes mellitus, log(NT-proBNP), treatment with ACE-inhibitors or ARBs, beta-blockers, or MRA (Supporting Information: Table S4).

3.5 | Sex hormones and prolactin

Serum gonadocorticoids and prolactin were analyzed separately between men and women. In postmenopausal women, there were no significant differences in total testosterone, estradiol, progesterone, and prolactin between HF patients and both control groups (Table 2 and Figure 4A–D). Hormone levels were under the lower assay detection limit in several women ($n = 5 < 0.09$ nmol/L for testosterone, $n = 35 < 18$ pmol/L for estradiol and $n = 5 < 0.1$ nmol/L for progesterone). No differences in these hormones were found between HFrEF and HFmrEF (data not shown).

In men, total testosterone was significantly reduced in HF patients compared to HC ($p = 0.01$; Table 2 and Figure 4A). No significant differences were found for estradiol, progesterone, and prolactin in men with HF versus controls (Table 2 and Figure 4F–H). Male HF patients on MRA had significantly higher progesterone levels compared to patients without (1.5 ± 0.8 vs. 0.9 ± 0.4 nmol/L, $p = 0.03$). No significant differences by MRA intake were found in female HF patients (data not shown). There were no significant differences in sex hormones between HFrEF and HFmrEF (data not shown). No association of testosterone with log(NT-proBNP), log(hs-troponin T), or LVEF was found in HF patients (Supporting Information: Figure S4G–I). In the total study cohort, testosterone was independently associated with sex, BMI, log(NT-proBNP), and treatment with ACE inhibitors or ARBs, but not age, smoking, LDL cholesterol, diabetes mellitus, eGFR, or treatment with beta-blockers or MRA (Supporting Information: Table S4).

TABLE 2 Hormone measurements in patients with HF and controls

Parameter	Healthy controls ($n = 62$)	Elevated risk for HF ($n = 54$)	Heart failure ($n = 52$)	p Value HC versus HF	p Value Risk versus HF
Thyroid hormones					
TSH (mU/L)	2.2 ± 0.8	2.0 ± 1.0	2.3 ± 1.6	0.97	0.37
fT3 (pmol/L)	4.8 ± 0.4	4.9 ± 0.5	4.7 ± 0.7	0.57	0.17
fT4 (pmol/L)	15.1 ± 2.1	15.5 ± 2.2	16.1 ± 2.3	0.05	0.34
fT3/fT4 ratio	0.33 ± 0.05	0.32 ± 0.05	0.30 ± 0.06	**0.03**	0.06
Catabolic hormones					
PTH (ng/L) (median [IQR 25%–75%])	46 (37–52)	47 (35–53)	59 (50–84)	**<0.001**[a]	**<0.001**[a]
Cortisol (nmol/L)	436 ± 108	404 ± 128	497 ± 150	**0.03**	**<0.001**
Sex hormones in females					
Testosterone (nmol/L)	0.5 ± 0.5	0.7 ± 0.7	0.6 ± 0.4	1.0	1.0
Estradiol (pmol/L)	27.7 ± 48.8	20.0 ± 20.5	12.1 ± 8.1	0.55	1.0
Progesterone (nmol/L)	0.6 ± 0.3	0.7 ± 0.5	0.7 ± 0.5	1.0	1.0
Prolactin (µg/L)	11.1 ± 5.4	10.8 ± 6.1	12.4 ± 6.6	1.0	1.0
Sex hormones in males					
Testosterone (nmol/L)	18.6 ± 5.3	16.7 ± 9.1	14.4 ± 6.6	**0.01**	0.49
Estradiol (pmol/L)	89.9 ± 28.5	102.1 ± 66.3	91.4 ± 41.1	1.0	1.0
Progesterone (nmol/L)	1.3 ± 0.7	0.9 ± 0.7	1.4 ± 0.8	0.99	0.07
Prolactin (µg/L)	9.5 ± 3.4	9.6 ± 5.6	10.1 ± 4.1	1.0	0.89

Note: Mean values ± standard deviation are shown unless otherwise specified. p-Values after adjustment for multiple comparisons are shown and significant values are only denoted with ANOVA or Kruskal–Wallis test was significant. Bold values denote significant results.

Abbreviations: ANOVA, analysis of variance; fT3, free triiodothyronine; fT4, free thyroxine; HC, healthy controls; HF, heart failure; IQR, interquartile range (25%–75%); PTH, parathyroid hormone; TSH, thyroid-stimulating hormone.

[a]Statistical analysis performed with logarithmic data.

4 | DISCUSSION

This study provides evidence for distinct abnormalities in the endocrine hormone profile of stable HF patients with reduced LVEF despite optimal disease-modifying treatment. HF patients exhibited a lower fT3/fT4 ratio, elevated PTH and cortisol levels as well as lower total testosterone compared to HC. Patients with EF < 40% (HFrEF) had significantly lower levels of fT3 compared to patients with LVEF 40%–49% (HFmrEF). Lower fT3 and higher PTH levels were independently associated with NT-proBNP, an important prognostic cardiac biomarker. In addition, fT3 was independently associated with troponin T, an indicator of chronic subclinical cardiac injury in HF patients.

4.1 | Thyroid hormones

Our findings of a reduced fT3/fT4 ratio, and reduced fT3 (HFrEF patients) but normal TSH levels are in line with previously published studies.[12–14] This profile is known as low T3 syndrome, euthyroid sick syndrome, or nonthyroidal illness syndrome and is often found in severe or acute illnesses but also in 20%–30% of HF patients.[15] In HF, low T3 levels and a reduced fT3/fT4 ratio correlate with the severity of the disease such as NYHA class,[14] adverse cardiac remodeling in echocardiography,[16] or the extent of fibrosis in cardiac MRI.[17] Several studies could also establish low fT3 as an independent predictor of mortality in HF.[14,18] Accordingly, we have found inverse associations of fT3 with the prognostic biomarkers NT-proBNP and hs-troponin T and positive associations with LVEF in multiple regression analysis in line with previously published evidence.[19,20] In contrast to disease severity, we had no indication that fT3 levels differed by HF etiology. Interestingly, higher body weight was associated with elevated fT3 in our cohort, a finding also described in previous studies.[21] Further studies should elucidate whether this endocrine phenomenon contributes to the "obesity paradox" in HF (improved prognosis of slightly obese patients).[22]

Whether low T3 syndrome represents a compensatory mechanism (i.e., physiologic reduction of metabolism in response to impaired cardiac output and systemic inflammation) or is an inherently maladaptive process that aggravates myocardial

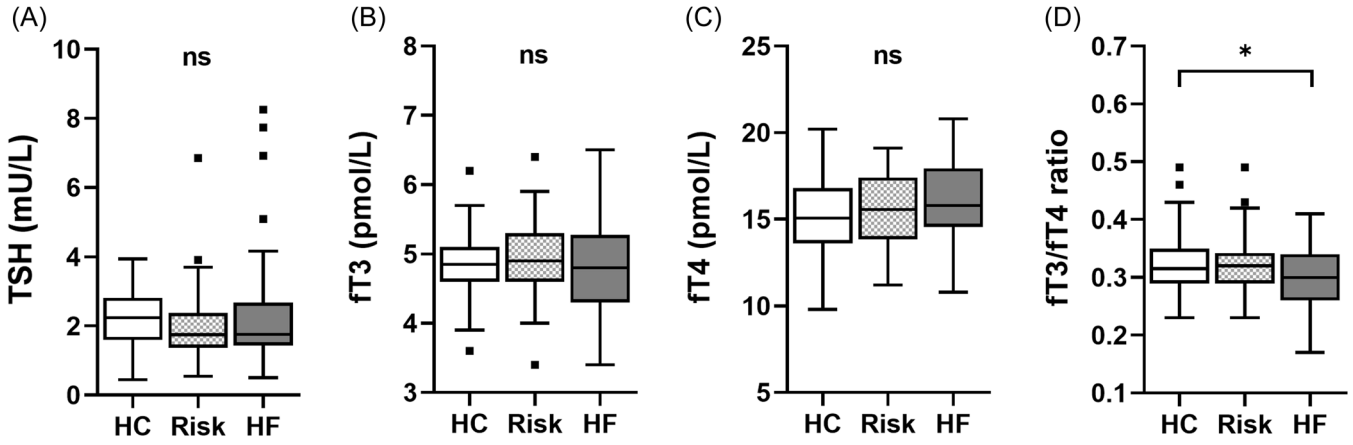

FIGURE 1 Thyroid hormones in patients with HF and controls. Box and whiskers plots (Tukey) are shown for TSH (A), free T3 (B), free T4 (C), and the fT3/fT4 ratio (D) in heart failure (HF) patients, patients at elevated risk for HF (Risk) and healthy controls (HC). ns, not significant. *$p < 0.05$.

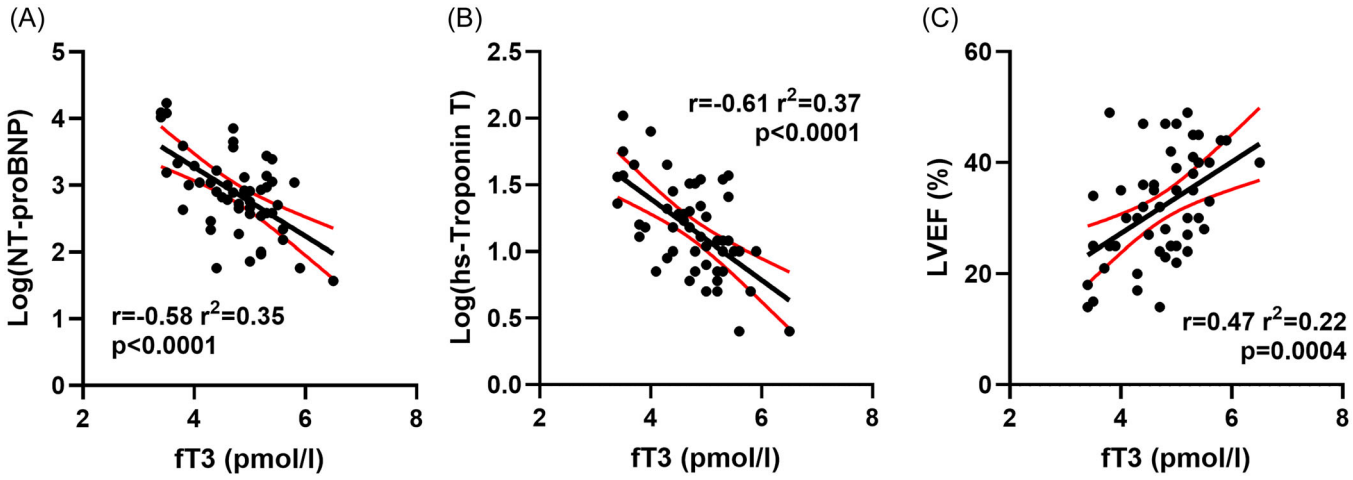

FIGURE 2 Correlation of fT3 with cardiac biomarkers and left ventricular ejection fraction (LVEF) in patients with HF. Correlations and linear regression (95% confidence intervals in red) are shown for logarithmized NT-proBNP (A), logarithmized high-sensitivity troponin T (B), and LVEF (C) with free T3 (fT3) in HF patients ($n = 52$). HF, heart failure.

dysfunction remains still elusive.[15] While preliminary evidence indicates that pharmacologic restoration of a euthyroid state with the active thyroid hormone liothyronine may be beneficial,[23–26] this awaits confirmation from definitive outcome trials.

4.2 | PTH

PTH plays a central role in calcium and phosphate homeostasis and bone metabolism. Chronically elevated levels on the other hand are associated with cardiovascular disease and mortality, possibly by increasing ectopic calcification, inflammation, and adverse cardiac remodeling.[27] We observed significantly increased levels of PTH in HF patients with reduced LVEF, in line with previous reports.[28] Calcium and phosphate levels in our cohort suggest that the increase in PTH is mostly secondary and not primary (glandular) in origin. An important trigger of PTH release is increased phosphate retention due to chronic kidney disease, which is a common and important comorbidity in HF patients. Interestingly, PTH was independently associated with NT-proBNP after accounting for renal function, pointing towards additional triggers of PTH release in HF beyond renal insufficiency.

Our finding of higher PTH in HF patients on loop diuretics may be an explanation, as RAAS activation is increased by loop diuretics and aldosterone is known to stimulate PTH release and vice versa.[29,30] Increased dietary phosphorous may also be an important trigger of elevated PTH, especially in the context of low dietary calcium intake. Future studies correlating PTH levels with dietary phosphorous intake in HF patients could provide useful evidence. Vitamin D deficiency is also known to increase PTH and low vitamin D levels are associated with HF in previous studies.[31]

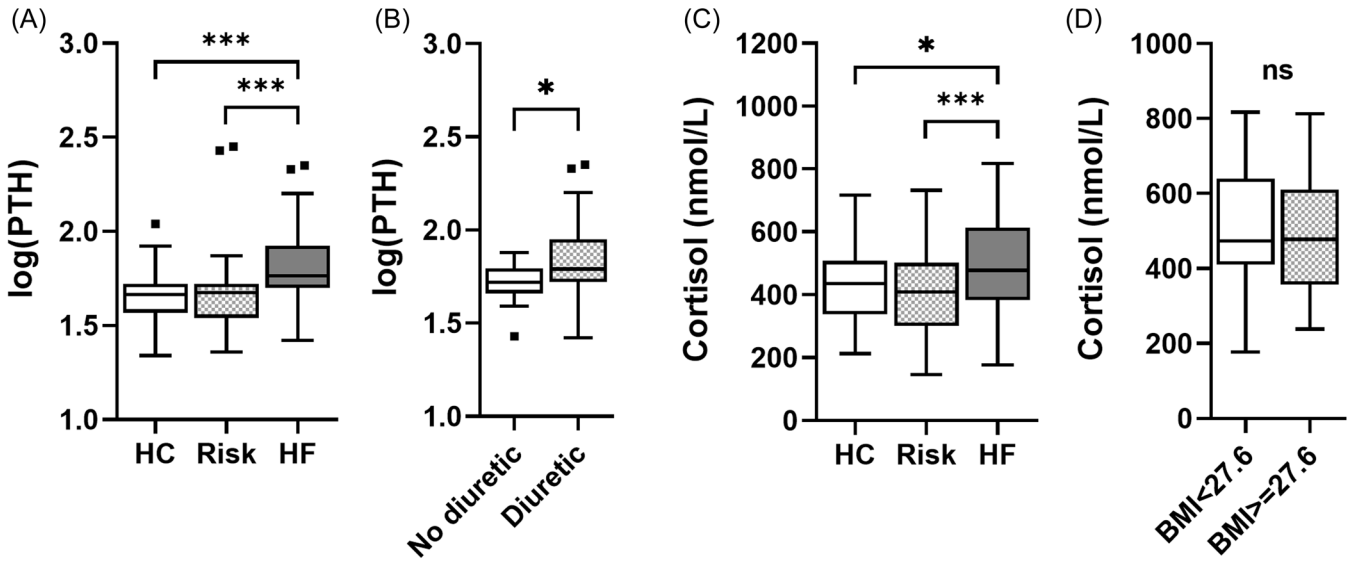

FIGURE 3 Parathyroid hormone and cortisol in patients with HF and controls. Box and whiskers plots (Tukey) are shown for the logarithmized parathyroid hormone (log[PTH]) in HF patients and controls (A), log(PTH) in HF patients with versus without loop diuretics (B), and morning fasting plasma cortisol in HF patients and controls (C) and cortisol in HF patients with BMI below versus at and above the median (27.6 kg/m^2) (D). *$p < 0.05$; ***$p < 0.001$. HF, heart failure.

4.3 | Cortisol

HF is also associated with an imbalance in anabolic and catabolic hormones, which may contribute to exercise intolerance, cardiac cachexia, and disease progression.[2] Our observation of elevated cortisol levels in HF patients mirrors data on patients with untreated HF.[6] Part of the increase in cortisol may be explained by comorbidities known to be associated with increased cortisol such as insulin resistance,[32] cardiac cachexia,[33] or ischemic heart disease.[34] We did not find differences in cortisol levels in patients with diabetes, CAD, or below median BMI. Cortisol can also be increased by spironolactone,[35] however there were no such differences in our study. Interestingly, a small study showed that cortisol and not aldosterone is displaced from the myocardium after infusion of MRA, suggesting that cortisol is involved in the adverse effects of mineralocorticoid receptor activation in the heart.[36] Accordingly, cortisol was found to be an independent predictor of death in MRA-naïve patients but not patients on MRAs.[37]

4.4 | Sex hormones and prolactin

With regard to sex hormones, lower levels of total testosterone and higher levels of cortisol fit into the concept of anabolic and catabolic imbalance in HF patients.[38] Lower levels of free testosterone have been described in HF patients[7] and low total testosterone is independently associated with mortality in HF patients.[39] Reduced testosterone has also been associated with the presence of CAD,[40] however, we found no differences in HF patients with versus without CAD that could explain the lower levels in our cohort. In our study, higher body weight (BMI) was associated with lower testosterone which is in line with the published literature on endocrine dysfunction in obesity.[41] The phenomenon of lower testosterone levels in patients on ACE inhibitors or ARBs as suggested by the regression analysis has also been previously described in the literature and may also contribute to the differences.[42] While small clinical trials demonstrated beneficial effects of testosterone replacement on exercise capacity in HF,[43] studies in broader non-HF populations indicated potential cardiovascular risks, and increased atherothrombotic events in particular.[44] This shows that the complex hormonal abnormalities in HF and cardiovascular disease are still incompletely understood.

We also investigated estradiol and prolactin, as both low and high estradiol levels (in men) and elevated prolactin were associated with adverse outcomes in HF.[8,9] No differences in estradiol and prolactin levels were found in the sex-stratified analysis and estradiol levels were below the assay detection limit in most postmenopausal women. Higher sample size and more sensitive assays are needed to draw more conclusions.

To our knowledge, our study is the first to report on serum progesterone in patients with HF. While we found no differences in progesterone levels in patients with HF overall, male patients on MRA had higher progesterone levels. This may be explained by the blockade of mineralocorticoid and progesterone receptors by MRAs as progesterone is known to bind to both receptors. Interestingly, progesterone has substantial antimineralocorticoid activity[45] leading to increased natriuresis[46] and potassium retention,[47] as well as possibly cardioprotective effects in preclinical studies.[48]

4.5 | Limitations

There are several limitations of our study: (1) The study was observational in nature. Therefore, residual confounding cannot

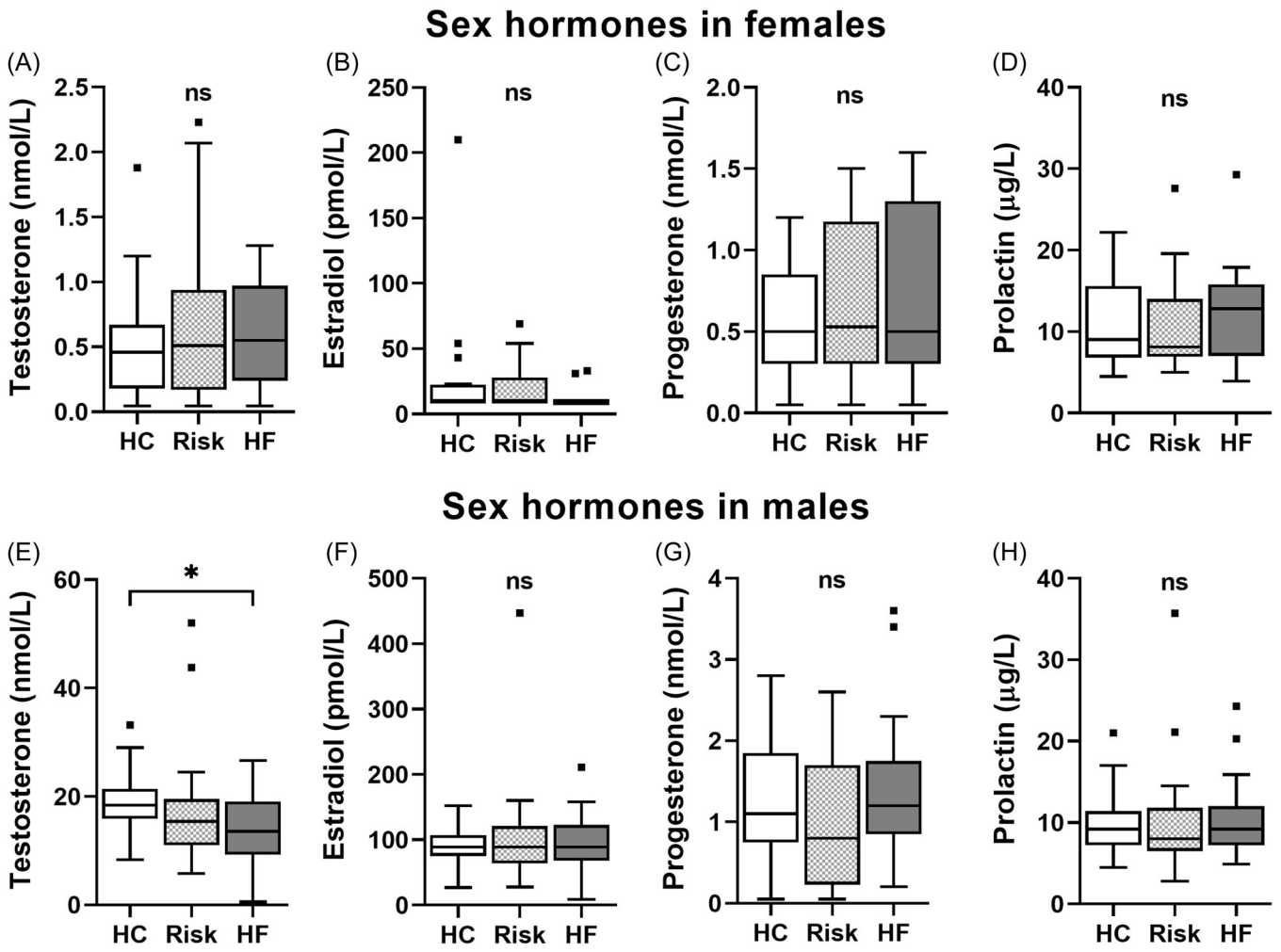

FIGURE 4 Sex hormones and prolactin in patients with HF stratified by gender. Box and whiskers plots (Tukey) are shown for sex hormones in females (upper panel) with testosterone (A), estradiol (B), progesterone (C), and prolactin (D) and in males (lower panel) with testosterone (E), estradiol (F), progesterone (G) and prolactin (H). Same groups and abbreviations as in Figure 1. ns, not significant. $^{**}p < 0.01$. HF, heart failure.

be excluded. We have included two different control groups with similar age, sex, and comorbidities to mitigate this. We also excluded patients with primary endocrinopathies, hormone replacement therapy, and amiodarone, as all these are known to affect hormone levels. (2) Due to missed sample size calculation, the power of the study, including all analyses may be affected. (3) Due to the cross-sectional design, we have no information on the temporal change in hormone levels, especially concerning untreated HF. (4) We have not analyzed associations with mortality outcomes as the sample size of our cohort was too small and follow-up time was limited. However, several previous studies have already reported that thyroid hormones, PTH, cortisol, and testosterone are important predictors in HF patients as described above. (5) Due to the sample size, this study has limited power for subgroup analyses such as LVEF subgroup, NYHA class, concurrent drug treatment or gender-stratified analysis of sex hormones. Likewise, the power for multiple regression analyses was limited. Therefore, we cannot fully exclude residual confounding by comorbidities or other potential differences between the study groups. A larger study sample is needed to more closely understand the complex interaction of endocrine hormones with comorbidities in HF patients.

5 | CONCLUSIONS

In this cohort of stable patients with HF and reduced EF, substantial differences in the endocrine hormone profile were found despite established disease-modifying therapies. Patients with HF and reduced EF were characterized by a lower fT3/fT4 ratio, elevated PTH and serum cortisol, as well as lower total testosterone levels in male patients. Levels of fT3 and PTH were independent predictors of NT-proBNP and thereby link endocrine abnormalities with markers of disease severity and prognosis in HF. Further studies should explore the complex relationship of HF with endocrine hormones beyond the classical neurohormonal axis.

AUTHOR CONTRIBUTIONS

Matthias P. Nägele: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Visualization; Writing–original draft; Writing–review and editing. **Jens Barthelmes**: Formal analysis; Investigation; Methodology; Resources; Software; Validation; Writing–review and editing. **Leonie Kreysing**: Conceptualization; Data curation; Investigation; Methodology; Writing–review and editing. **Thomas Haider**: Formal analysis; Validation; Writing–review and editing. **Delia Nebunu**: Investigation; Resources; Visualization; Writing–review and editing. **Frank Ruschitzka**: Funding acquisition; Project administration; Supervision; Validation; Writing–review and editing. **Isabella Sudano**: Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing–review and editing. **Andreas J. Flammer**: Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing–review and editing.

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CONFLICTS OF INTEREST

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DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and/or its supplementary materials.

TRANSPARENCY STATEMENT

The lead author Matthias P. Nägele affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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