Endocrine (2019) 65:714–716
https://doi.org/10.1007/s12020-019-01993-y

RESEARCH LETTER

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Human heart shifts from IGF-1 production to utilization with chronic heart failure

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Received: 21 May 2019 / Accepted: 22 June 2019 / Published online: 2 July 2019

Chronic heart failure (CHF) is characterized by multiple hormonal and metabolic deficiencies (MHD) [1, 2]. In this context, abnormalities of growth hormone (GH) and its effector insulin like growth factor-1 (IGF-1) play a distinct and relevant role [3, 4]. Circulating levels of IGF-1 have been associated with cardiovascular events and mortality in CHF, but the benefit of the use of IGF-1 as prognostic marker in CHF is still unresolved [5]. Stimulation of IGF-1 receptors by the hormone can occur in response to the plasma circulating IGF-1 or to the local paracrine/autocrine production. Cardiomyocytes are able to produce IGF-1 mRNA and experimental conditions of heart hypertrophy are associated with an increase in such production, suggesting that modulation in local IGF-1 production might be an adaptive response to the need of local growth [6]. However, no data are available on the handling of IGF-1 by the human heart in vivo in healthy subjects or in patients with CHF. Thus, aim of the current study was to clarify whether human heart in vivo is an organ that generates or rather extracts IGF-1 and whether in patients with CHF there was a change in IGF-1 handling by the heart. For this purpose, we studied the difference in IGF-1 concentrations between aorta and coronary sinus in patients with or without CHF. In addition, we also evaluated inflammatory cytokine plasma glucose concentrations and their transcoronary concentration gradients (TCG).

Methods

Consecutive patients with or without clinical diagnosis of CHF and undergoing elective coronary angiography were recruited and enrolled in the study. CHF patients were affected by ischemic/non-ischemic CHF diagnosed according to the guidelines [7]. The patients without CHF (control group), were affected by factual or alleged stable coronary artery disease with no signs of CHF. Both populations had to have stable medication for at least 6 months. Before any diagnostic procedure was performed, blood samples were simultaneously obtained from coronary sinus (CS) and ascending aorta (Ao) and collected in pre-chilled Vacutainer tubes containing sodium citrate. After centrifugation, plasma samples were stored at −80 °C until assayed. Plasma concentration of IGF-1 and cytokines (IL-1β, IL1-Rα, IL-4, IL-5, IL-6, IL-7, IL-9, IL-10, IL-12, IL-13, IL-17, and TNFα) was measured by Bioplex-Technology. The relative TCG were calculated as the difference between CS and Ao concentrations. Therefore, a positive TCG would indicate net release of the IGF-1/cytokine from the heart, whereas a negative value would rather represent a net extraction by the heart. Categorical

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Table 1 Demographic, clinical characteristic, and plasma levels of IGF-1 of the patients studied

	CHF ($n = 11$)	CTR ($n = 10$)	p-value
Age (yrs)	66.5 ± 11-8	62.8 ± 6.9	0.38
Sex (M/F)	10/1	6/4	0.25
EF (%)	41.2 ± 5.6	56.5 ± 4.7	<0.001
BMI (kg/m^2)	27.6 ± 2.6	28.9 ± 2.3	0.30
SBP (mmHg)	140.5 ± 18.3	145.5 ± 18.7	0.56
DBP (mmHg)	83.0 ± 7.1	86.1 ± 7.0	0.35
HR (%)	62.7 ± 12.7	67.7 ± 10.8	0.39
eGFR (mL/min)	82.0 ± 48.2	104.4 ± 29.6	0.25
Hb (g/dL)	13.1 ± 1.8	13.7 ± 1.8	0.45
Ao IGF1 (ng/mL)	117.2 [84.8–151.1]	91.6 [69.3–124.6]	0.20
SC IGF1 (ng/mL)	94.3 [85.8–149.4]	95.7 [68.8–130.7]	0.47
TCG (ng/mL)	−2.4 [−8.1–0.33]	12.9 [0–22]	<0.05

CHF chronic heart failure, *CTR* control subjects, *EF* ejection fraction, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, *EGFR* estimated glomerular filtration rate, *Hb* haemoglobin, *SC* coronary sinus, *Ao* aortic root

variables were expressed as counts and percentages. Normally distributed continuous variables were expressed as mean ± Standard Deviation whereas continuous data with skew distributions were expressed as the median and interquartile range [IQR]. Groups were compared using the Student *t*-test and Mann-Whitney U-Test as appropriate. A p-value of <0.05 was considered statistically significant. Statistical analysis was performed using the R statistical programming environment, Version 3.5.

Results

Eleven CHF patients and ten non-HF subjects (CTR group) were enrolled in the study. Demographic and clinical characteristics of the study population are depicted in Table 1. No differences were observed between CHF and CTR group except for left ventricular ejection fraction (LVEF) (41.2 ± 5.6 *vs* 56.5 ± 4.7, $p < 0.001$).

Compared to CTR patients, CHF patients showed higher, although non-statistically significant, IGF-1 Ao levels [91.6 (69.3–124.6) and 117.2 (84.8–151.1) ng/mL], whereas the CS concentrations were similar in the two groups [95.7 (68.8–130.7) and 94.3 (85.8–149.4) ng/mL, respectively). Therefore, whereas patients without CHF showed a positive TCG [12.9 (0–22) ng/mL], indicating net release of IGF-1 by the heart, patients with CHF were characterized by a negative TCG [−2.4 (−8.1–0.33) ng/mL] pointing to a net uptake of IGF-1 ($p < 0.05$). In contrast with the heart of patients with CHF that showed a negative TCG and the need of extracting circulating IGF-1 for its functioning, CTR patients showed a TCG above zero, suggesting strongly that their heart is capable of producing much more IGF-1 than necessary locally.

Arterial and coronary concentration of all cytokines was within the normal range in the two groups. As a consequence, TCGs for all the above-mentioned cytokines were similar in CHF and CTR patients (data not shown).

Discussion

We show for the first time in humans in vivo that the heart of subjects without CHF is a contributor to the circulating pool of IGF-1, exerting the role of a true endocrine organ. Since we did not measure coronary blood flow, we cannot exactly quantify the entity of such contribution or dissect the relative component of TCG, i.e. cardiac production from local consumption of IGF-1 (circulating or locally produced). However, since the concentration of IGF-1 in the CS exceeds the one in the arterial bed (positive TCG) the concept that the IGF-1 produced by the heart overcomes the amount of the growth factor locally used appears undisputable. In patients with CHF, studied during optimized and stable therapy, a substantial shift of the way the heart handles the IGF-1 is evident. The concentration of IGF-1 in the CS is lower than the concentration in the aorta, i.e. the TCG changes to negative, therefore, the heart subtracts IGF-1 from the circulating pool. For the reasons discussed above, we cannot establish whether the shift toward a negative TCG is due to an increase in the heart IGF-1 utilization or a decrease in its production or the combination of the two. What we can affirm is that the amount of IGF-1 locally used is higher than the amount produced. From experimental model and data in vitro, the presence of myocardial hypertrophy or frank HF associates with an increase in IGF-1 mRNA content, pointing from one side to an increased production of IGF-1, from the other side suggesting an increased need of the IGF-1 by the derailing organ, in order to compensate the damage occurred after the cardiac insult and/or promote the survival of unaffected cells [6]. We might speculate that CHF induces a local extreme need of IGF-1 so that the heart becomes a utilizer rather than a producer. In our own data, increased cardiac production of IGF-1 is perfectly compatible with the shift from a positive to a negative TCG: the amount of IGF-1 taken-up by the heart largely exceeds the amount produced by the same organ, whatever it is.

Low circulating IGF-1 levels have been associated with systemic and local release of pro-inflammatory cytokines (IL-1β, TNF-α, and IL-6) [8]. In addition, in experimental studies, IGF-1 gene transfection reduces the mRNA expression of IL-1β and TNF-α [9]. In our population, circulating inflammatory biomarkers and TCG were comparable in patients with or without CHF. This is not

surprising since the patients studied were in stable clinical conditions.

In the context of CHF as MHD, hormonal replacement therapies are gaining increasing attention as possible adjuvant therapeutic approaches [10, 11].

Our data show that the heart of patients with CHF requires much more IGF-1 than normal, suggesting that after the exogenous supply of GH, the increase of IGF-1 would fulfil a profound need of the failing organ. Therefore, a better understanding of cardiac handling of IGF-1 would substantiates such an approach and improve our knowledge of its pathophysiological relevance.

Acknowledgements A. Salzano received research grant support from Cardiopath, UniNA and Compagnia di San Paolo, as part of the Programme STAR. AM. Marra was supported by an institutional grant from Italian Healthcare Ministry (Ricerca Finalizzata for young researchers). (Project n. GR-2016-02364727).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval The study protocol was conducted according to the Declaration of Helsinki and was approved by the Federico II University Ethics Committee.

Informed consent Informed consent was obtained from all subjects included in the study.

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