INSULIN RESISTANCE IN PATIENTS WITH CHRONIC

HEART FAILURE

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ABSTRACT

Insulin resistance may be present in patients with heart failure and has a potential to reduce

myocardial as well as skeletal muscle activity. We have assessed insulin resistance as measured by

fasting insulin resistance index (FIR!) in 23 patients with chronic heart failure (CHF) [9 valvular

disease, 6 DCM and 8 IHD] and 10 control subjects of similar age and BMI. Fasting glucose, insulin,

C-peptide and lipid profile were estimated. CHF patients had similar mean fasting plasma glucose

concentration to control but significantly higher mean plasma insulin (10.57 vs 6.14 mU//L, P< 0.001)

and C-peptide (119.4 vs 63.2, P <0.001). Significant insulin resistance could be detected in patients

with CHF as assessed by FIR! (P <0.001 vs control). Analysis of variance showed that FIR1 was not

related to the etiology of CHF but to its severity as awased by NYHA functional classification (P <

. 0.05). Both EF% and CI were not correlated to FIR!. Our fmdings show that patients with CHF are

• insulin resistant with increased insulin secretion and hyperinsulinetnia compared to matched healthy

sedentary control group. The degree of insulin resistance was correlated to severity of heart failure

(NYHA classification) but not to ventricular systolic pump dysfunction or the cause of CHF. The

mechanisms underlying insulin resistance in these cases as well as possible therapeutic implications

, remain to be further investigated in future studies.

INTRODUCTION hemodynamics, functional status and

metabolic factors including

Insulin resistance is a peculiarly

neuroendocrine and immunological

ubiquitous phenomenon. About 25% of processes. Recent evidence has

apparently healthy people may be

suggested that metabolic factors may

considered to be insulin resistant.

be of greater importance than the more

Moreover, it has been found to be a

conventional assessment of

feature in a diverse range of disorders

hemodynamic status and clinical

including non—insulin dependent

features(3). Insulin resistance has been

diabetes mellitus, obesity and

implicated in several potentially

hypertension (22,13).

adverse metabolic changes which can

The primary goals for treatment

affect energy and blood flow to both

of chronic heart failure (CHF) are

the myocardium and skeletal

improvements in survival and quality

muscle(9). Thus, it could contribute to

of life. Several factors are predictive of

both the progressive deterioration of

impaired survival in CHF. The main 3

myocardial function and the peripheral

independent areas of importance are

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clinical features that are central to the

syndrome of CHF. Few published

cardiamyopathy in 6 cases. The

diagnosis of ischemic heart was based

studies suggested the presence of on history of previous acute

• insulin resistance in severe CHF cases

(29, 35, 39).

The purpose of the present

work is to establish whether insulin

resistance is common in CHF and to

investigate its possible association with

the severity or the cause of CHF in

these cases.

PATIENTS AND METHODS

A) Patients:

:This study was carried out at

the Internal Medicine & Cardiology

department and laboratories of Zagazig

and Benha University Hospitals. It

comprised 2 groups of cases.

Group (I) were 23 cases of

CHF with impaired LV pump function

as evidenced by EF% <35% in

echocardiography for at least 6

months. They were clinically stable on

treatment that was not changed in the

last 8 weeks. The mean ± SD of the

duration of CHF was 26 ± 9 months.

According to the NYHA functional

classification. 4 were in class I, 8 in

(class II), 5 (class III) and 6 were in

class (IV). The main etiology of heart

failure was ischemic heart disease in 8,

valuvlar heart disease in 9 and dilated

myocardial infarction or coronary

angiography. Dilated cardiornyopathy

and valvular heart disease were

diagnosed on basis of

echocardiography. All patients were on

fursemide (at least 40 mg P.0/ daily)

and an ACEI, Digoxin, aspirin, nitrate

and amiodarone were used in some of

them. None of these drugs is known to

have any effect on lipid, insulin or

carbohydrate metabolism although

ACEI might improve insulin

sensitivity. The control group (II)

comprised age, sex and body mass

index [BMI] — matched normal

population. They were on no

medication, sedentary in life and with

normal oral glucose Tolerance test.

Demographic criteria of both studied

groups are summarized in Table (I).

An informed consent was given by all

cases.

B) Methods:

(i) All cases were subjected to

full history taking and thorough

clinical evaluation. None had signs of

fluid overload, raised jugular venous

pressure, peripheral or pulmonary

edema.

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(ii) Routine laboratory

investigations included complete blood

count (Coulter T890), serum sodium,

potassium, calcium and magnesium,

liver function tests, blood urea, serum

creatinine and creatinine clearance by

(autoanalyzer Hitachi, 908) in addition

to oral glucose tolerance test. Cases

showed abnormal results were

excluded.

(iii) An ECG and chest X-ray

as well as echocardiographic

assessment of structural and functional

Status of the heart were done for all

cases. Coronary angiography was done

in 6 patients with CHF.

**(iv) Collection of samples for**

**biochemical determinations:** All cases

came after 12 hours fasting (morning

medications were also omitted). Venous

blood sample was taken on EDTA and

immediately placed on ice, centrifuged

and stored in aliquots at —25 °C. Plasma

glucose (37), total cholesterol (IC) (1),

triglycerides (TG) (26), LDL —

cholesterol (LDL-C)(12) and HDL

cholesterol (HDL-C)(18) were measured.

Plasma insulin was determined by

radioimmunoassay (RIA) method (42)

using a kit supplied from *Diagnostic*

*Products Corporation (Los Angeles-*

*USA),* and C-peptide level was

determined by RIA method (19) using a

kit supplied from *Immunotech (France).*

**(v) Statistical analysis:** Data was

expressed as mean ± SD. Student's t test

was used to compare the mean values

between 2 groups and ANOVA was used

if in between more that 2 groups.

Pearson's correlation coefficient (r) was

computed to predict correlation between

variables. Values of P < 0.05 were

considered significant.

**RESULTS**

**Both** studied groups were

comparable as regards the age, sex and

BMI. They had similar plasma levels

of total cholestrol (TC) and low

density lipoprotein cholestrol (LDLC).

Fasting plasma triglycerides (TG)

were higher and plasma high density

lipoprotein cholestrol (HDL-C) were

decreased in CHF cases compared to

healthy controls (Table I). Fasting

plasma glucose levels were within

normal in both groups. Despite,

significantly increased mean fasting

plasma insulin (172%). C-peptide

(188%) concentrations in CHF group

versus normal control (P <0.001).

The estimated mean fasting

insulin resistance index (FIRI) was

significantly higher (179%) in CHF

cases denoting a considerable degree

of insulin resistance among CHF

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resistance to the insulin's metabolic

effects does not necessarily equate

with an equal degree of resistance to its

cardiovascular effects. In addition, it

has been recently speculated that

insulin resistance (with 'reduced

availability of glucose as an energy

source for skeletal muscle cells) may

be important in reducing skeletal

musc16 strength and increasing

fatiguability in CHF patients (4)•

Indeed, the mechanisms of both

insulin resistance and insulin's

vasodilatory effects remain uncertain.

A number of mechanisms for insulin

resistance have been suggested in

various conditions including

abnormalities of the interaction

between insulin and its receptor (17),

increased sympathetic nervous system

activity (14) and in hypertension,

pressure-induced restriction of the

microcirulation (15). *Paolisso et al.*

(29) suggested that insulin resistance

may be related to increased free fatty

acid levels secondary to increases in

plasma noradrenaline levels. Similarly,

there has been much speculation as to

what mechanism may underlie insulin's

vasodilatory actions. It has been

suggested that insulin might regulate

the local release of endotheliumderived

nitric oxide. The

administration of N-monomethyl Larginine,

a specific inhibitor of nitric

oxide synthetase abolished insulininduced

vasodilation (31), (32). One

possible mechanism for insulin

regulation of nitric oxide-mediated

vasodilatation is indirect via the

inhibition of lipolysis and the

consequent decrease in free fatty acids

circulating levels (33). Other work has

suggested the involvement of beta

adrenergic mechanisms(10), or a more

direct action on vascular smooth

muscle cells (43), perhaps via insulin's

known effect on Na-K ATPase

activity(30).

The cause(s) of insulin

resiStance and insulin's vasodilator

effects remains unknown and it was

not directly addressed during this

work. Thus, it remains uncertain

whether this insulin resistance is a

primary or secondary phenomenon in

heart failure. However, findings in our

work support the presence of insulin

resistance in chronic stable heart

failure cases regardless its etiology or

severity. The clinical importance of

these observations lies in a possible

therapeutic intervention in these cases

to overcome the pathogenetic

mechanisms responsible for these

phenomena and thus improve survival

and quality of life of these patients.

Can exogenous insulin or insulin*U.*

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analogue be of therapeutic interest in

this condition? A hotly debated issue

and a compelling question that remains

to be answered in future studies.