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Improved cardiac performance with human calcitonin gene related peptide in patients with congestive heart failure

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Abstract

Study objective **– The aim of the study was to assess the cardiovascular effects of human calcitonin gene related peptide (CGRP) in patients with congestive heart failure.**

Design **– The effects of CGRP II (or β), 12.5 $\mu g \cdot h^{-1}$, given by intravenous infusion for 24 h to digitalised patients with congestive heart failure, were assessed by measurement of cardiac functional indices.**

Patients **– Five patients (four female) were studied. Age was 73-82 years. Three were in New York Heart Association phase III and two in phase IV.**

Measurements and main results **– The pre-ejection period to left ventricular ejection time ratio and the QT distance adjusted for heart rate were lowered by 21% and 4% respectively. The left ventricular shortening index was raised by 43%. The arterial pressure and heart rate did not change consistently.**

Conclusion **– Calcitonin gene related peptide improves myocardial contractility in patients with congestive heart failure. This is the first time this has been shown.**

Congestive heart failure is usually caused by reduced cardiac output as a result of impaired myocardial contractility. Its treatment includes positive inotropic agents, eg, digitalis, as well as vasodilator and diuretic therapy.[1] Calcitonin gene related peptide (CGRP) is a recently discovered neuropeptide with potent cardiovascular effects that include positive chronotropic and inotropic actions on the heart, vasodilatation, and hypotension.[2–9] The stimulation of the heart rate and coronary vasodilatation presumably depend on the local release of CGRP from afferent nerve fibres in the heart induced by capsaicin and interaction with receptors linked to cyclic adenosine monophosphate (AMP).[10–16] The improved ventricular contractility of CGRP was suppressed in normal human subjects through blockade of adrenergic receptors, and may be driven by reflex sympathetic stimulation.[4] Here we show evidence of improved ventricular contractility with CGRP as recorded with non-invasive techiques in five digitalised patients with congestive heart failure.

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Methods

We studied four female and one male patient aged 73 to 82 years with congestive heart failure, three in New York Heart Association phase III and two in phase IV.[17] Four patients had coronary artery disease and the fifth had hypertrophic cardiomyopathy. Body weight was 44-66 kg, and height 147-158 cm. Informed consent about the experimental treatment with CGRP was obtained from all patients, and the study was approved by the appropriate ethics committee.

The patients were treated with oral β-methyldigoxin (Lanitop, Boehringer, Mannheim, W Germany), 0.6 mg (0.77 nmol) per day for three days, followed by 0.3 mg (0.39 nmol) per day for four days (figure), after which they were given human CGRP II (or β) (Peninsula Laboratories, Belmont, CA, USA), 12.5 $\mu g \cdot h^{-1}$ (3.3 nmol) by intravenous minipump infusion for 24 h.

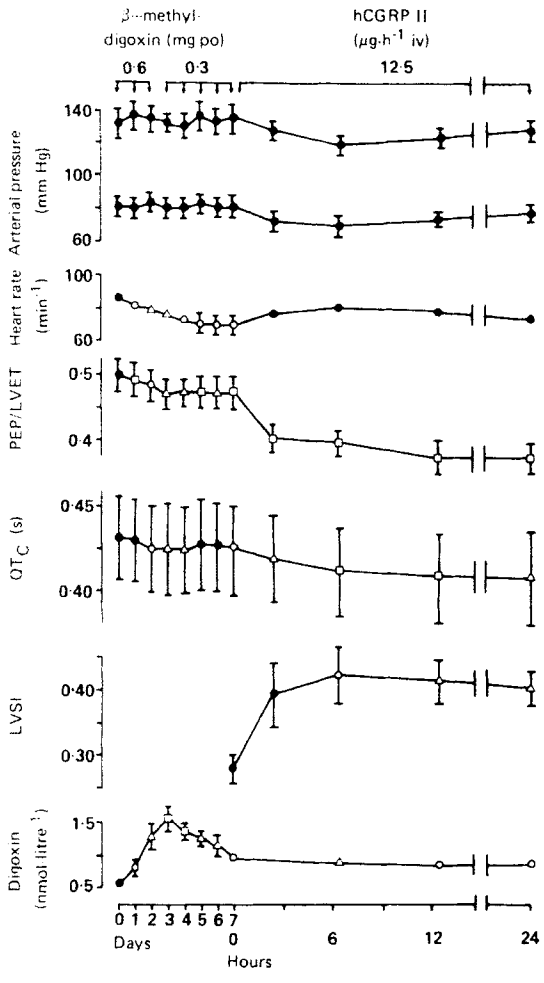
The systemic arterial pressure was monitored continuously by intra-arterial manometry. The duration of the pre-ejection period and the left ventricular ejection time were determined using electrocardiography, phonocardiography, and external carotid pulse tracings.[18] The corrected QT interval (QT_c) was calculated by dividing QT by the square root of the preceding R-R interval. The left ventricular cavity was measured before and during the infusions with CGRP by M mode echocardiography at the end diastolic and the end systolic filling times.[19] The left ventricular shortening index was calculated as the ratio between the left ventricular end diastolic minus the end systolic diameters, and the left ventricular end diastolic diameter.

Serum concentrations of digoxin were measured by radioimmunoassay.[20] Total serum calcium was measured by atomic absorption spectrophotometry (Perkin-Elmer, Norwalk, CN, USA).[21]

Statistical analysis was by paired t test.[22] Values are given as means (SEM).

Results

Congestive heart failure was treated with β-methyldigoxin and therapeutic serum concentrations (0.7-1.8 nmol·litre^{-1}) were achieved (figure).[20] The heart rate was lowered ($p<0.05$), but the pre-ejection period to left ventricular ejection time ratio and the QT_c intervals were only minimally decreased, from 0.50 (SEM 0.02) to 0.47(0.02) ($p<0.01$), and from 0.43(0.03) s to 0.42(0.03) s, respectively ($p<0.01$). Myocardial contractility remained largely unchanged during the seven day treatment with therapeutic doses of β-methyldigoxin. As a result, the patients were essentially refractory to treatment with digoxin. No other treatment was used.



Effects of peroral (po) β-methyldigoxin and intravenous (iv) human CGRP II (hCGRP II) on arterial pressure, heart rate, pre-ejection period to left ventricular ejection time ratio (PEP/LVET), the QT distance adjusted for heart frequency (QT_c), the left ventricular shortening index (LVSI), and serum concentrations of digoxin in five patients with congestive heart failure. Each value represents the mean, bars=SEM. Open symbols represent statistically significant changes from the values obtained at the start of the study, or in the case of the left ventricular shortening index from before the administration of CGRP (○, $p<0.05$, △, $p<0.01$, □, $p<0.001$), closed symbols (●, $p>0.05$).

Human CGRP II was then given as an intravenous infusion for 24 h at a rate previously used in normal subjects.[23] The arterial pressure was minimally lowered and the heart rate remained slightly raised ($p>0.05$), but the pre-ejection period to left ventricular ejection time ratio was lowered from 0.47(0.03) to 0.37(0.03) (normal <0.35; $p<0.001$), and the QT_c intervals were shortened from 0.42(0.03) to 0.41(0.03) s ($p<0.01$). The left ventricular shortening index was raised from 0.28(0.02) to 0.42(0.04) (normal >0.29; $p<0.01$). Improved contractility of the heart ventricle was evident with CGRP in all the five patients. With the dose of CGRP used, the undesired hypotensive and positive chronotropic effects were limited and did not affect the therapeutic efficacy of CGRP on ventricular contractility. All five patients noted subjective improvements. With CGRP, serum calcium levels remained unchanged: before CGRP 2.29(0.03) mmol·litre^{-1}; after CGRP 2.29(0.04) mmol·litre^{-1}.

Discussion

The improvement of myocardial contractility is a principal object of the treatment of congestive heart failure. Digitalis has limited efficacy and potential toxicity. β Adrenergic agonists are thought to exert positive inotropic effects on the heart through stimulation of cyclic AMP production.[1] As a result, calcium influx is stimulated in myocardial cells.[24] The improved ventricular contractility of CGRP was suppressed in normal subjects through blockade of adrenergic receptors, and may result in part from reflex sympathetic stimulation.[4] Coronary vasodilatation is achieved through interaction of CGRP with its receptors and stimulation of cyclic AMP production.[6 7 13 15 16]

Here we have used non-invasive procedures. Reduction of systolic time intervals is brought about through positive inotropic agents and reduction in afterload, eg, due to vasodilatation.[18] The combined positive inotropic action on the heart and vasodilator properties of CGRP explain the improvement of congestive heart failure in the present patients. In view of the vasodilator activity of CGRP it remains to be shown whether cardiac function is also ameliorated through the positive inotropic action of the peptide[25] in patients with congestive heart failure.

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