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Prevention to Intervention

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Impaired Cerebrovascular Reaction to Adrenergic Stimulation in Congestive Heart Failure

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Abstract: An impaired cerebral pressure autoregulation has been reported in hypertensives but has never been described in congestive heart failure (CHF). The cerebrovascular reaction to a pressor adrenergic stimulus induced by isometric handgrip (HG) was studied in 10 NYHA Class III CHF patients (57 to 70 yrs, mean 63), 10 elderly (60 to 69 yrs, mean 64.5) and 10 young (21 to 31 yrs, mean 24.5) healthy subjects. Mean flow velocities in the middle cerebral arteries (MCA V_{mean}) [transcranial Doppler], mean arterial blood pressure (ABP)[Finapres], and end-tidal CO_2 (Et-CO_2) [Capnograph] were studied during 3 consecutive periods (5 minutes baseline; 90 second handgrip, 10 minute recovery). (Et-CO_2) was unaffected. MCA V_{mean} did not change during HG dependent pressure increase; on the contrary MCA V_{mean} significantly rose in CHF patients ($p<0.001$ and $p<0.01$ vs baseline in the right and left MCAs) and increased less in the elderly ($p<0.05$ and $p<0.02$ vs baseline in the right and left MCAs). Therefore pressure autoregulation was intact in the young while it was impaired in CHF patients more than in the elderly.

Introduction

The chronic reduction of cardiac output caused by heart failure sets in motion a wide array of cardiac and vascular reactions aimed at maintaining a constant blood supply to vital organs. These changes result in a redistribution of blood flow to the coronary and cerebral circulations at the expense of other regions such as the splanchnic and cutaneous

vessels (1,2). Despite these feed-back mechanisms, patients with severe cardiac failure have a lower cerebral blood flow when compared to healthy individuals (3) and often show different forms of mental deterioration ranging from a reduced mnemic function to more severe cognitive impairment. The improvement of cardiac performance usually leads to the resolution of neuropsychological symptoms and to a incresed cerebral blood flow (4-6); the low cardiac ouput, however, does not entirely account for the onset of cognitive impairment that can arise independently from any worsening of heart dysfunction. Chronic cardiac failure is associated with a reduced cerebral vasomotor reserve capacity (7) but it is not known whether this abnormality translates into a defect of cerebral pressure autoregulation. If present such a defect may play a role in causing a neural damage similar to what has been observed in hypertensives (8,9), in head injured patients (10) and in other disease conditions characterized by wide fluctuations in cardiac output (11). The aim of this study was to define the characteristics of cerebral pressure autoregulation in patients with severe (NYHA Class III) congestive heart failure (CHF) and to assess whether they are different from those of the young and elderly healthy.

Experimental Procedure

Autoregulation can be estimated noninvasively by inducing a sustained pressor response to adrenergic stimulation (static or steady state autoregulation) or by inducing the release of thigh cuffs (dynamic autoregulation) and observing the middle cerebral velocity response. Comparison studies have revealed that both methods of testing yield similar results (12). In the present investigation the autoregulation has been studied by evaluating with transcranial Doppler the cerebrovascular response to a 35% maximal voluntary right handgrip, a standardized adrenergic stimulation commonly used for this purpose (13-15). The stimulus is known to elicit a blood pressure increase by a reflex stimulation of circulating norepinephrine release (16-17). The simultaneous monitoring of MCA velocity and of other physiologic parameters such as arterial blood pressure and end–tidal CO_2 provides a real time picture of the interaction of the main factors affecting cerebral vasomotion. Before beginning all measurements each subject remained in a supine position in a silent room for a 30 minute stabilization period. After a 5 minute baseline period all subjects performed a 90 sec right isometric handgrip stimulation. The handgrip was followed by a recovery period that lasted until all hemodynamic variables had reverted to baseline.

Subjects

10 patients affected by NYHA Class III CHF patients were studied (aged 57 to 70 years; mean age 63). The results were compared with the data observed in 10 young healthy (age 21 to 31 yrs, mean 24,5), and 10 healthy elderly subjects (age 60 to 69 yrs,mean 64,5) contemporaneously studied by the same experimental protocol and already described elsewhere (11). All subjects were non smokers, had a bmi $\leq$ 27, and were not offspring of diabetic or hypertensive patients because the vascular response to sympathetic stimulation has been found to be altered in these patients (18). None of the subjects was taking oral contraceptives. Patients were admitted to the study if CHF had been diagnosed by clinical examination or by echocardiographic or other instrumental evaluation (chest radiography or cardiac radioisotopic scanning). Exclusion criteria included diabetes, hypertension, and orthostatic hypotension. In all subjects hemodynamic carotid disease had been excluded by carotid ultrasound examination (2D echo and Duplex) before testing. The types of heart disease underlying cardiac failure were ischemic heart disease in 7 patients, dilated cardiomyopathy in 2 patients and valvular heart disease in 1 patient. Patients were studied during a period of hospitalization; angiotensin converting enzyme inhibitors were withdrawn 48 hours before testing cerebral hemodynamics. Soon after drug suspension all patients received close clinical surveillance. Only those whose conditions had remained stable after the 12 hour drug withdrawal period were admitted into the study and completed the 48 hour wash-out period according to the study protocol. All subjects refrained from assuming antiinflammatory drugs for 15 days before being examined and any other medication active on vascular tone. All subjects had given their informed consent before participating in the study according to the declaration of Helsinki.

Materials and methods. Cerebral hemodynamics was bilaterally investigated with transcranial Doppler (MultiDop x 4 DWL) by measuring the mean velocity in the middle cerebral artery (MCA V_{mean}) through the temporal windows by two 2 MHz probes. Arterial blood pressure (Finapres) and end-tidal CO_2 (Datex Normocap CO_2 monitor) were simultaneously recorded.

Statistical Analysis

Results are expressed as mean values $\pm$ SD. Student t-test for independent samples was used to compare the mean baseline values of the three groups. The effects induced by handgrip on each variable were evaluated according to a 2-step statistical analysis: first an ANOVA for repeated measures was used to evaluate the variations among periods;

second a post-hoc (least significant difference) was used to detect the differences of values at different times versus baseline. Statistical significance was set at $p<0.05$

Results

Baseline blood pressure values were lower in CHF patients than in young and elderly healthy subjects ($p<0.05$ and $p<0.05$ vs. young group respectively, Tab. 1). In the elderly subjects and in CHF patients baseline velocities were similar and significantly lower than in the young (Tab. 1). Handgrip induced a significant blood pressure increase in all groups (+11 mmHg, $p<0.001$ vs baseline in CHF patients; +19 mmHg, $p<0.005$ vs. baseline in the elderly; +13 mm Hg, $p<0.05$ vs. baseline, in the young, least significant difference test, ANOVA). End-tidal CO_2 remained constant in all subjects. The individual examples shown in Fig. 1 provide an accurate picture of the different patterns of autoregulation observed in the three groups. During handgrip mean velocities did not change in the young whereas they rose steeply in the CHF patient and more slightly in the elderly subject. The mean MCA V_{mean} increased only during the stimulus in patients (+16.3%, $p<0.001$; +15.6%, $p<0.01$ vs. baseline in the left and right MCA respectively); in the eldery subjects the increase in MCA V_{mean} peaked during HG but reverted to baseline only after the second minute of the recovery period ($p<0.02$, +23%, $p<0.05$ +20% vs baseline in the left and right MCAs).

Table. I Baseline mean arterial blood pressure and mean velocities in the middle cerebral arteries of the young and elderly groups and CHF patients.

	Young (n=10)	Elderly (n=10)	CHF patients (n=10)
ABP (mm/Hg)	93.9±13.5	101.5±15.4	80.9± 13.8
	*	*	
MCAL V_{mean}(cm/sec)	61.3±12.9	44.5±3.5	46.0± 11.6
	*	*	
MCAR V_{mean}(cm/sec)	62.1±10.	43.8±8.9	37.4± 14.2
	*	*	

ABP, mean arterial blood pressure; MCAL V_{mean}, mean velocity of the left middle cerebral artery; MCAR V_{mean}, mean velocity of the right middle cerebral artery. *$p<0.05$.

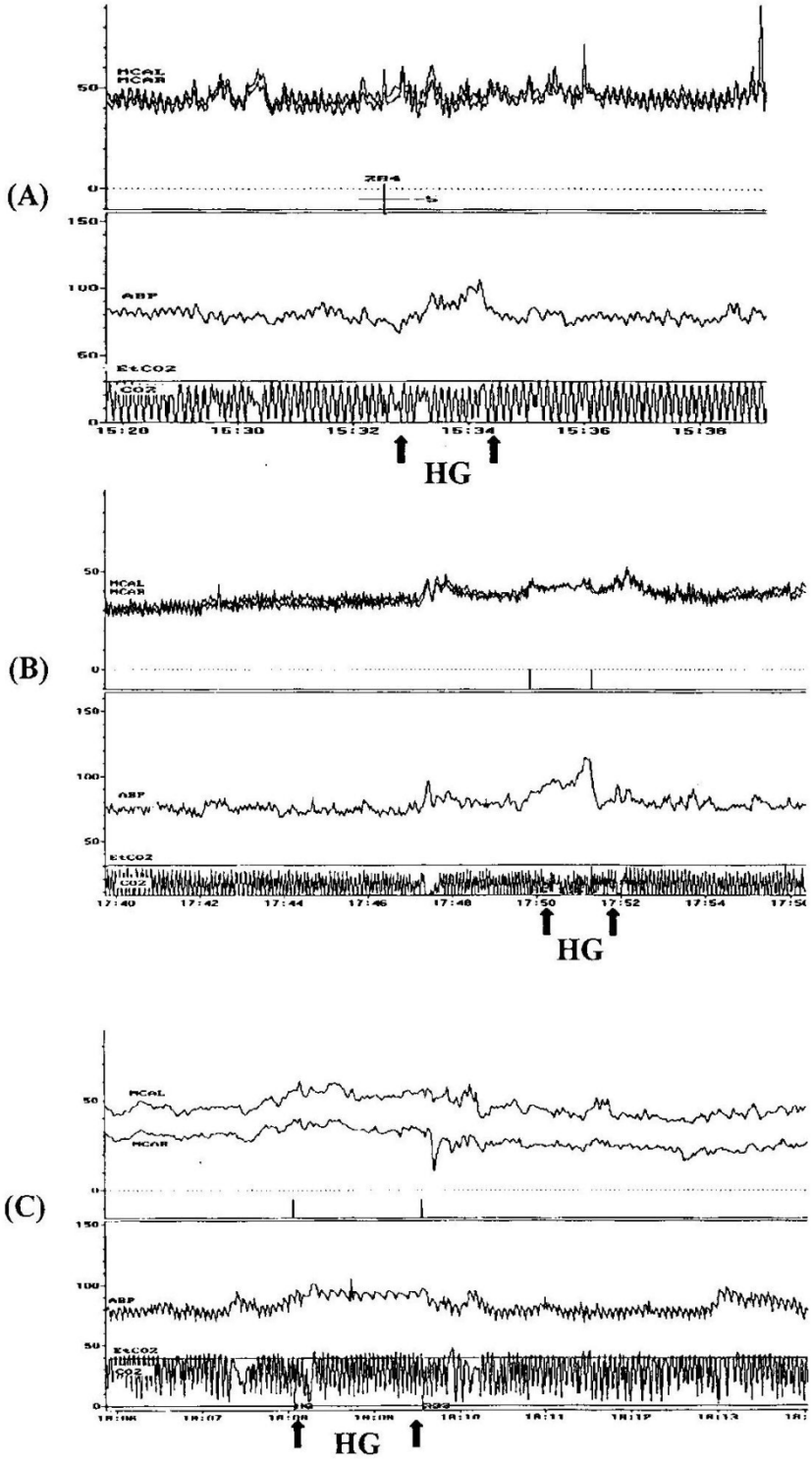

Figure 1. Effects of blood pressure increase during handgrip (HG). Three different patterns of autoregulation can be observed: no velocity change during HG in a young subject with intact autoregulation (A); velocity slightly increases in an elderly healthy subject with partially reduced autoregulation (B); velocity steeply increases parallel with the surge of arterial blood pressure in a patient with congestive heart failure with severely impaired autoregulation (C).
MCAL= mean velocity in the left middle cerebral artery; MCAR = mean velocity in the right middle cerebral artery; ABP = mean arterial blood pressure; Et CO_2 = end-tidal CO_2

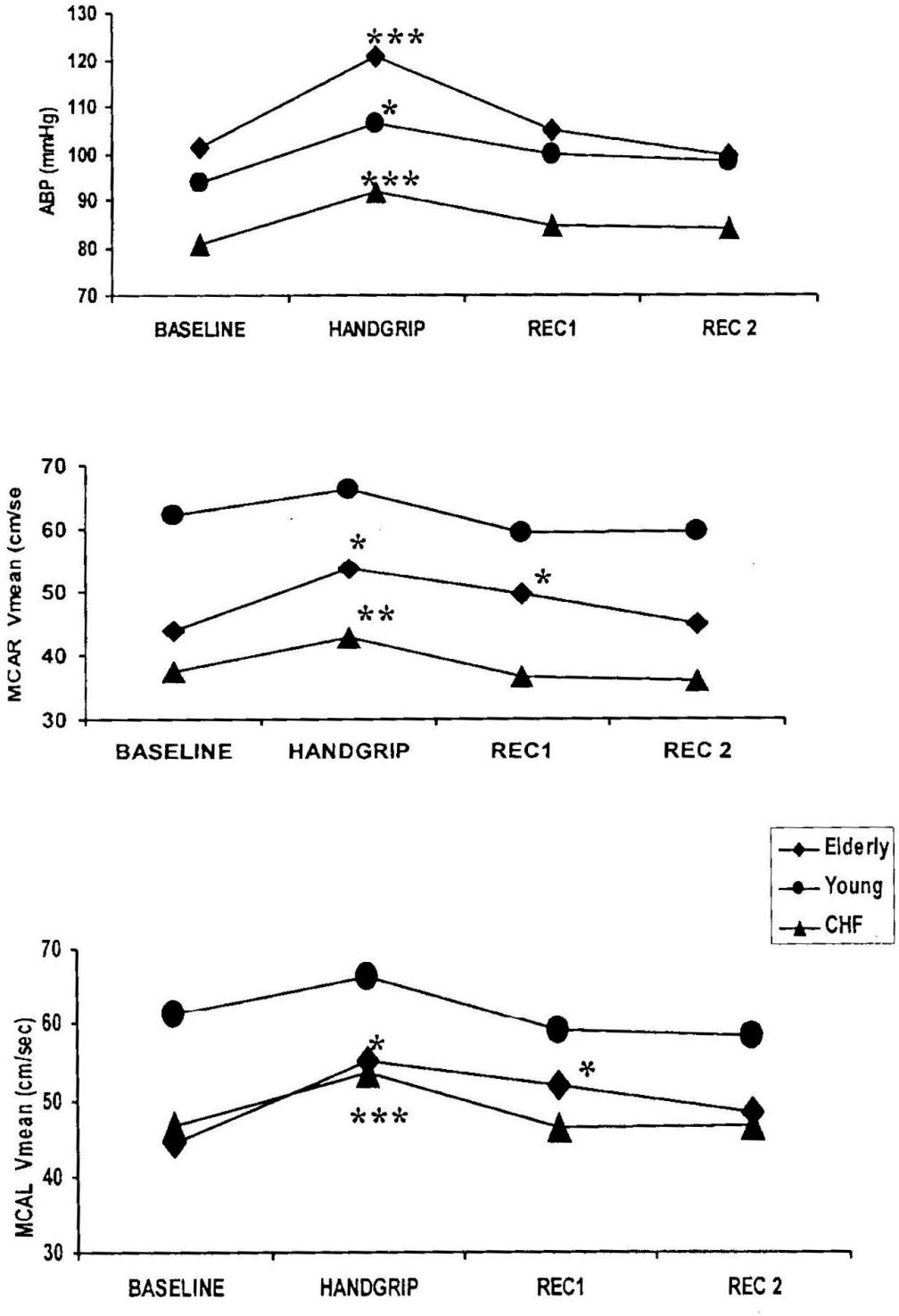

Figure 2. Effects of isometric handgrip on mean arterial blood pressure (ABP), and cerebral hemodynamics.
*MCAL V_{mean}, mean velocity in left middle cerebral artery; MCAR V mean, mean velocity in right middle cerebral artery. Data are mean values of each period. Baseline = 5 minute baseline period; Handgrip = 90 second right hand isometric contraction; Rec 1 = 2 minute recovery; Rec 2 = 8 minute recovery. *p<0.05 vs baseline; **p<0.01 vs baseline; ***p<0.005 vs baseline (least significant difference test, ANOVA)*

Conclusions

The isometric handgrip that we have used has induced a significant and sustained blood pressure increase consistent with an effective adrenergic stimulation. The changes in arterial blood pressure were all within the limits of autoregulation (19). While in the healthy young individuals the effects of blood pressure increases have been easily offset by an intact pressure homeostasis, in the others the rise in pressure was not effectively buffered by a vasoconstrictive reaction; these findings may indicate that both the healthy elderly and the patients with severe CHF have an impaired pressure autoregulation. In the CHF, however the loss of the autoregulatory mechanisms can pose a more serious threat to the nervous system given that even minor blood pressure increases can cause significant changes in cerebral bood flow. This pressure–passive cerebral vascular bed makes it more vulnerable in front of the wide fluctuations of cardiac ouput and arterial blood pressure often observed in CHF patients. Our study do not provide any conclusion on the mechanisms underlying the loss of autoregulation. However an hyperstimulation of the sympathetic nervous system and the renin-angiotensin activation have been documented both in the elderly and in CHF patients (21-23) and may have a role in this abnormality. Indeed it has already been demostrated that angiotensin enzyme inhibition resets cerebral autoregulation at lower blood pressure and can increase cerebral blood flow in patients with cardiac failure (3,23).

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