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Cardiovascular adaptation to mudpack therapy in hypertensive subjects treated with different antihypertensive drugs

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Abstract. – OBJECTIVE: In selected hypertensive subjects, cardiovascular adaptation to warm environments may be inadequate or even harmful: heating associated to mudpack therapy may cause unexpected hypotension. How different antihypertensive drugs may affect the cardiovascular response to mudpack therapy is poorly studied.

AIMS: To evaluate the effects of β-blockers and angiotensin II receptor antagonists/ACE inhibitors on the acute cardiovascular adaptation to mudpack treatment in SPA in elderly hypertensive patients.

PATIENTS AND METHODS: Thirty-one elderly subjects were divided in normotensive subjects (N; n=10) and hypertensive patients treated with ACE-inhibitors/Angiotensin II receptor antagonists (HTA; n=12) or with selective β_1-blockers (HTB; n=9). Systolic (SBP) and diastolic (DBP) blood pressure were continuously recorded (10 min) in supine position, immediately before and during mudpack treatment (40°C). Heart rate (HR), stroke volume (SV), cardiac output (CO) and total peripheral resistance (TPR) were assessed.

RESULTS: During mudpack treatment SBP did not significantly change in both HTA and N groups (132±11 and 112±13 mmHg, respectively), but significantly decreased in HTB (111±18 mmHg, $p < 0.01$ vs baseline) patients. HR increased in all groups (HTA: 72±10 bpm; HTB: 65±6 bpm; N: 70±10 bpm; $p < 0.01$ vs baseline). A significant reduction ($p < 0.01$ vs baseline) in SV and CO occurred in HTB, but not in HTA and N groups. TPR significantly increased in HTB (1335±464 dyn·s·cm^{-5}, $p < 0.01$ vs baseline) but not in HTA and N subjects (1389±385 dyn·s·cm^{-5} and 1245±323 dyn·s·cm^{-5}, respectively).

CONCLUSIONS: Mud treatment did not cause relevant haemodynamic changes in normotensive and HTA-treated hypertensive subjects. Conversely, β-blocking treatment apparently limited the cardiovascular adaptation to thermic stress, through a possible reduction in myocardial contractility, thereby, causing a significant decrease, although not dangerous, in systolic blood pressure.

Key Words:
β-blockers, ACE-inhibitors, Angiotensin II receptor antagonists, SPA therapy.

Introduction

Hypertensive subjects often develop an autonomic dysfunction and a blunted cardio-vagal baroreflex sensitivity[1,2]. This may reduce adaptation of cardiac output and vascular peripheral resistances to warm environments: consequently, the exposure to high environmental temperature or a hot bath immersion may trigger a marked hypotension or even cause sudden death[3]. Moreover, ageing is known to worsen such phenomena[4].

Elderly people typically attend SPA (*Salus Per Aquam*) centers: SPA therapy includes non-pharmacological approaches such as balneo-therapy, hydrotherapy and mudpack treatment[5,6]. In particular, mudpack therapy consists in the local application or whole body immersion in mud, and is currently recommended to alleviate joint pain occurring in patients with rheumatic diseases[7,8,9] and muscular pain disorders[10]. Mudpack produces a pain-relieving effect by a local hypertermia in the underlying tissues[11,12]. As SPA environments are usually characterized by high temperature and humidity, hypertensive elderly patients may be at risk for acute hypotension during SPA attendance. Indeed, several studies previously demonstrated an increased risk for orthostatic hypotension, syncope and cardiovascular death during sauna, Turkish hammam and other SPA procedures, especially in elderly people[13]. Similarly, hot mud treatment (consisting in 10-20 min of mud immersion at a temperature of about 40°C) may cause an acute severe hypotension in elderly hypertensive patients, although specific studies on this issue are

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still lacking. Moreover, the effect of antihypertensive therapy on acute cardiovascular adaptation to warm environments was poorly investigated. This is particularly relevant especially for those antihypertensive agents that may cause and maintain peripheral vasodilation, as the newer generation β-blockers with ancillary vasodilating properties (carvedilol, nebivolol, etc.)[14] and the angiotensin II antagonists (both ACE-inhibitors and angiotensin II receptor antagonists)[15].

This study aimed at evaluating the different effects of β-blocking drugs and ACE inhibitors/angiotensin II receptor antagonists on the acute cardiovascular adaptation to mudpack treatment in elderly hypertensive patients.

Patients and Methods

Subjects

Thirty-one elderly (> 65 years) subjects were recruited at the SPA station of the Ermitage Terme Bel Air Medical Hotel in Padua, Italy. Participants were divided into 3 groups: (1) normotensive subjects (N, n=10); (2) hypertensive patients treated with ACE-inhibitors/angiotensin II receptor antagonists (HTA, n=12); (3) hypertensive patients treated with third generation selective β-blockers nebivolol or carvedilol (HTB, n=9). Exclusion criteria were: uncontrolled hypertension, an acute coronary event or angioplasty within 6 months, atrial fibrillation, premature ventricular complexes, history of diabetes mellitus, central nervous system diseases or other conditions that could affect autonomic function. Drug therapy was administered at the standard dosage for hypertension, and no patients showed systolic (SBP) or dyastolic (DBP) blood pressure pathologic values at preliminary evaluation.

Participants were fully informed about the aims and procedures of the study, and gave their written consent to participate in the study, in agreement with the Declaration of Helsinki. The study protocol was approved by local Ethics Committee (University of Milan).

Experimental Procedures

Assessments were performed in the morning (between 6:00 and 9:00 AM). Subjects were asked to consume nothing except small amounts of water within 2 hours before the study, and to drink no caffeinated beverages or alcohol within 12 hours before the testing procedure. The whole experimental session took place in a SPA treatment room, kept at constant temperature (22°C). Physiological measurements were performed in two phases: in the first one, the subjects lied resting in supine position for 10 minutes. In the second phase, subjects underwent the application of warm mud (about 40°C) to the whole body (excluding head) for 10 min, in supine position.

Measurements

During both experimental phases, a 3-leads electrocardiogram (MP100, Biopac Systems Inc., Goleta, CA, USA) was continuously recorded at 1000 Hz frequency. Arterial blood pressure was recorded by a non-invasive pletismographic system (Finometer® Pro, Amsterdam, the Nederlands) applied to a hand finger. The acquired data were extracted from the Finometer® Pro device by a custom program (Beatscope® Easy software) at the end of each experimental session, and stored in a protected database for offline analysis. Finally, ectopic beats and artefacts were manually edited in each recorded signal.

Cardiovascular Parameters Analysis

SBP and DPB were continuously monitored. Mean arterial pressure (MAP) was obtained as the integral of pressure signal between the current and the following upstroke. Heart rate (HR) was calculated from the RR peak-to-peak series by an automated peak-finder procedure applied to the acquired ECG signal. Stroke volume (SV) was derived by integrating the aortic flow over one heart cycle[16]. Cardiac output (CO) was computed as the product of SV and HR. The cardiac index (CI) was, then, derived as the ratio between CO and the estimated body surface area (BSA) of each individual. Finally, total peripheral resistances (TPR) were calculated as the ratio MAP/CO.

Statistical Analysis

Where not otherwise stated, data are presented as mean ± standard deviation (m±SD). All variables were first analyzed using the Kolmogorov-Smirnov test, to verify the normality of data distribution. A two-way analysis of variance (ANOVA) with repeated measures and a post-hoc Fisher's Least Significant Difference test for multiple comparisons were used to evaluate the null hypothesis of the absence of changes in cardiovascular parameters observed in the two experimental phases (supine resting state and mudpack treatment) in normotensive and treated hypertensive subjects. The statistical significance was set at $p < 0.05$.

Results

Subjects

Table I shows the anthropometric and demographic features and SBP/DBP baseline values of the enrolled subjects.

Blood Pressure

Figure 1 (panel A) shows the values of SBP in the two experimental phases in N, HTA and HTB groups. In resting supine position, SBP showed higher values in HTA and HTB groups (130 ± 12 and 124 ± 10 mmHg, respectively) compared to N subjects (115 ± 11 mmHg, $p < 0.01$). During mudpack treatment SBP did not significantly change in both HTA and N groups (132 ± 11 and 112 ± 13 mmHg, respectively), but significantly decreased in HTB patients (111 ± 18 mmHg, $p < 0.01$ vs baseline).

Similarly, DBP (Figure 1, panel B) showed slightly higher values in HTA and HTB patients (83 ± 4 and 80 ± 8 mmHg, respectively) than in N subjects (75 ± 4 mmHg) in baseline conditions ($p < 0.01$). During mudpack treatment, DBP did not significantly change in both HTB and N groups (80 ± 14 and 77 ± 7 mmHg, respectively), but significantly increased in HTA patients (87±6 mmHg, $p < 0.01$ vs baseline).

Heart Rate

Figure 2 shows HR values during the two experimental phases in all groups. In resting supine position, HR was significantly lower in HTB group (55 ± 9 bpm) compared to HTA and N subjects (66±10 and 63±10 bpm, respectively, $p < 0.01$). During mudpack treatment, HR significantly increased in all groups (HTA: 72 ± 10 bpm; HTB: 65 ± 6 bpm; N: 70 ± 10 bpm; $p < 0.01$ vs baseline for all comparisons).

Table I. Demographic and anthropometric characteristics of the enrolled subjects, and baseline values of systolic (SBP) and diastolic (DBP) blood pressure (standard sphygmomanometry).

	HTA	HTB	N
n	12	9	10
Age, years	69 ± 4*	65 ± 4	61 ± 3
Gender (males/females)	6/6	2/7	2/8
Weight, kg	77± 3	76 ± 5	67 ± 2
Height, cm	169 ± 3	164 ± 3	164 ± 3
SBP, mmHg	135 ± 3*	127 ± 4*	116 ± 2
DBP, mmHg	81 ± 2*	81 ± 2 *	76 ± 1

N: normotensive subjects; HTA: hypertensive patients treated with ACE-inhibitors or angiotensin II receptor antagonists; hypertensive patients treated with β-blocking agents (HTB). *$p < 0.05$ vs N.

Stroke Volume, Cardiac Output and Cardiac Index

The relative changes in SV, CO and CI between baseline conditions and mudpack treatment are reported in Table II. The reduction observed in each parameter was significant in HTB group only ($p < 0.01$ vs baseline).

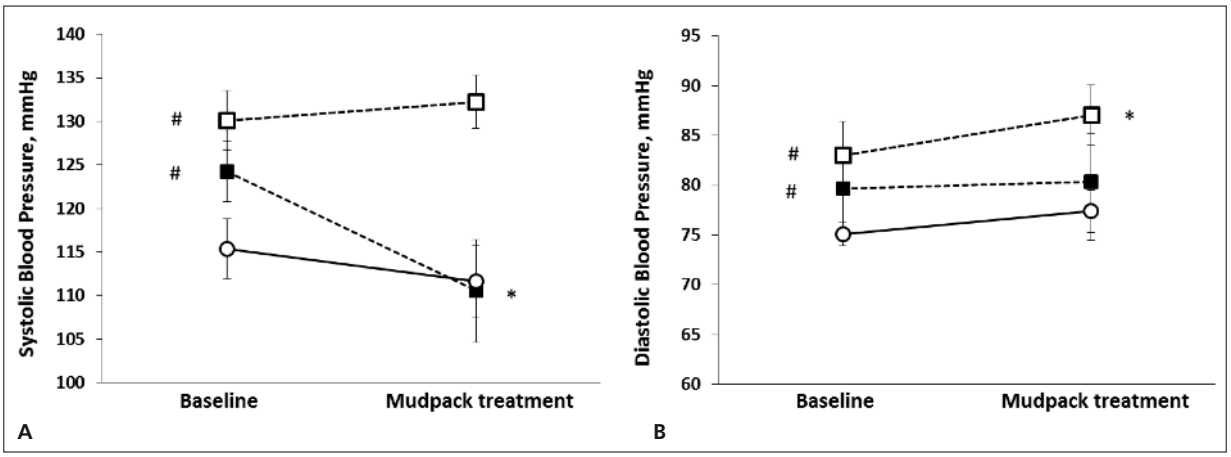

Figure 1. Changes (m ± MSE) in systolic (SBP, **panel A**) and diastolic (DBP, **panel B**) blood pressure from baseline condition (resting supine position) to mudpack treatment (10 min each). Open circles and continuous line: normotensive subjects (N); black squares and dashed line: hypertensive subjects treated with β-blocking agents (HTB); open squares and dashed line: hypertensive patients treated with ACE inhibitors or angiotensin II receptor antagonists (HTA). #$p < 0.05$ vs normotensive subjects; *$p < 0.05$ vs baseline.

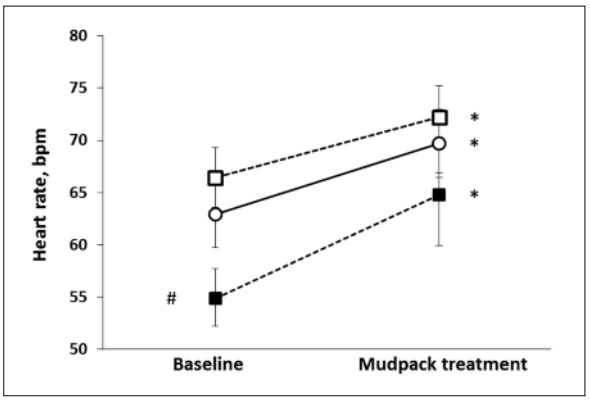

Figure 2. Heart rate (HR) changes (m ± MSE) from baseline condition (resting in supine position) to mudpack treatment (10 min each). Open circles and continuous line: normotensive subjects (N); black squares and dashed line: hypertensive subjects treated with β-blocking agents (HTB); open squares and dashed line: hypertensive subjects treated with ACE inhibitors or angiotensin II receptor antagonists (HTA). $^{\#}p < 0.05$ vs normotensive subjects; $^{*}p < 0.05$ vs baseline.

Total Peripheral Resistances

Figure 3 shows the values of TPR in both experimental conditions in all groups. In resting supine position, TPR were significantly lower in HTB group (1089 ± 105 dyn·s·cm^{-5}) compared to HTA and N subjects (1261 ± 208 and 1248 ± 404 dyn·s·cm^{-5}, respectively, $p < 0.01$). During mudpack treatment, TPR significantly increased in HTB group (1335 ± 464 dyn·s·cm^{-5}, $p < 0.01$ vs baseline) but not in HTA and N subjects (1389 ± 385 dyn·s·cm^{-5} and 1245 ± 323 dyn·s·cm^{-5}, respectively).

Discussion

This study investigated the acute hemodynamic effects of mudpack therapy in normotensive subjects and in hypertensive patients treated with different blood pressure lowering agents. We observed that the passive external heating caused by mudpack therapy slightly altered cardiovascular system homeostasis both in hypertensive and in normal subjects.

First, mudpack exposure led to an increase in HR (+13%, on average) in all tested groups (Figure 2). This confirms previous literature data on other typical SPA treatments, which cause passive external heating of the body: for example, a significant increase in HR was previously observed at the end of a sauna session in both normotensive[17] and hypertensive[18] patients. It is not clear whether HR increment is due to a reduction of parasympathetic tone or, on the contrary, to an increase in adrenergic stimulation. However, the fact that in our patients such HR adaptation was not blunted by β-blocking agents (a significant HR increase was detectable in all tested groups), suggests that it is probably a consequence of an inhibition of the vagal tone. HR was significantly lower in HTB group at baseline, confirming, as expected, that β-blocking drugs chronically reduce also the effect of basal sympathetic tone on the heart, compared to the other anti-hypertensive drug class.

Concerning blood pressure, although the risk of a marked blood pressure fall was shown to be higher in patients with hypertension receiving antihypertensive drugs[19], our results suggest that

Table II. Percentage changes between mudpack treatment and baseline condition for stroke volume (SV), cardiac output (CO) and cardiac index (CI).

	HTA	HTB	N
SV, % $D_{baseline\text{-}mudpack}$	-9.0 ± 3.0	-31.9 ± 5.1*	-12.1 ± 2.5*
CO, % $D_{baseline\text{-}mudpack}$	-1.8 ± 0.5	-18.3 ± 3.2*	-1.7 ± 0.4
CI, % $D_{baseline\text{-}mudpack}$	-2.1 ± 0.6	-19.8 ± 3.0*	-1.1 ± 0.3

HTA: hypertensive patients treated with ACE-inhibitors or angiotensin II receptor antagonists; hypertensive patients treated with β-blocking agents (HTB). $^{*}p < 0.05$ vs baseline.

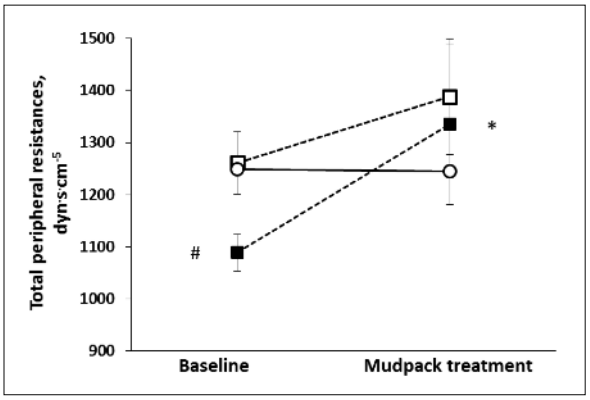

Figure 3. Changes (m ± MSE) in total peripheral resistances (TPR) from baseline condition (resting in supine position) to mudpack treatment (10 min each). Open circles and continuous line: normotensive subjects (N); black squares and dashed line: hypertensive subjects treated with β-blocking agents (HTB); open squares and dashed line: hypertensive subjects treated with ACE inhibitors or angiotensin II receptor antagonists (HTA). $^{\#}p < 0.05$ vs normotensive subjects; $^{*}p < 0.05$ vs baseline.

the two different classes of blood pressure lowering agents investigated may elicit different cardiovascular adaptation to external thermal stress (Figure 1). Indeed, heat exposure due to mudpack therapy did not cause significant blood pressure changes in both normotensive subjects and hypertensive patients treated with ACE-inhibitors or angiotensin II receptor antagonists. On the contrary, SBP was significantly reduced in HTB patients. In addition, mudpack application caused a significant fall in SV and CO, and a significant increase in TPR, in patients treated with β-blockers only. We hypothesized that this could be due to the specific β_1-adrenergic blockade of the heart, which could have limited myocardial contractility. Our patients were treated with nebivolol or carvedilol, newer generation adrenergic receptor antagonists with selectivity for β_1-receptors[20,21]. Furthermore, nebivolol causes peripheral vasodilatation via interaction with the endothelial L-arginine/nitric oxide pathway[22,23] and carvedilol causes vasodilatation via the β_1-adrenergic blockade[24]. These pharmacological properties appear to be associated with better tolerability compared with traditional β-blockers[25]. However, during passive heating induced by mudpack therapy a particular challenge for the hypertensive heart occurs. From a physiologic viewpoint, the skin vasculature dilates, with a subsequent rise of cutaneous perfusion, in order to decrease body core temperature through superficial heat dispersion. Consequently, a series of hemodynamic modifications follows, including increase of CO, mainly via HR and SV rise, and a concomitant decrease in TPR, secondary to vasodilation. In normotensive subjects and in hypertensive patients treated with ACE-inhibitors or angiotensin II receptor antagonists these physiological adaptations to heat stress seem not to occur, suggesting that the possible fall in SBP due to the increased cutaneous vasodilation was promptly balanced by an increase in HR, sufficient to keep CO unchanged. This finding confirms previous published data, which demonstrated that the augmented cardiac output is mainly due to the heat stress-induced increase in HR, since SV is typically unchanged or only slightly elevated[26,27]. Stroke volume was not modified also during other typical SPA treatment inducing heating, as sauna[28,29], Finnish bath and Turkish hammam[30]. Other experimental studies suggest that these warming procedures induce an increase in cardiac contractility[31], supporting the hypothesis that heat stress may increase the inotropic tone of the heart[32,33]. However, in our HTB patients the selective blockade of heart β_1-receptors may have blunted such increase in myocardial contractility. Therefore, the inotropic tone of the heart likely remained unchanged during thermal stress in these subjects. This may have caused a significant reduction in SV (-31%) and, thereby, in CO (-18%) (Table II). This latter reduction was probably limited, compared to that of SV, by the concomitant increase in HR observed in HTB group, probably due to a sudden parasympathetic deactivation. This might explain the consequent significant reduction of SBP (-11%) observed in HTB patients. At that point, the baroreflex mechanisms may have activated the peripheral vascular innervation to limit blood pressure fall. Hence, TPR resulted significantly elevated (+20%) in the HTB group (Figure 3): such increase has been observed, despite the possible peripheral vasodilation induced by the β-blocking agents at exam.

Conclusions

This study showed that the hemodynamic responses to passive heating due to mudpack treatment were modest in N and HTA groups, suggesting that heat stress induced by such thermal procedure is of limited magnitude. Therefore, this therapy may be considered safe in hypertensive subjects treated with non β-blocking drugs. Conversely, a particular attention is to be paid to patients treated with third generation β-blockers with ancillary vasodilating properties, as the possible reduction in cardiac contractility induced by these drugs may limit the cardiovascular adaptation to thermic stress, causing a significant fall in SBP. A close monitoring of blood pressure response to passive heating should, therefore, be a critical step in the preliminary clinical evaluation of hypertensive patients undergoing mudpack therapy.

The Finometer® Pro device uses the validated three-element algorithm of Windkessel, named Modelflow®, to compute the aortic flow waveform from the arterial blood pressure pulsation[34]. Modelflow® is currently considered a reliable method to assess changes in SV[16], but the absolute values of this parameter are not estimated to be fully reliable. For this reason, we did not provide absolute data, but only relative changes from baseline values, for SV parameter and for the subsequent calculations of CO and CI.

Due to various co-morbidities, most patients enrolled in this study were on poly-pharmacologic therapy. Although particular attention was paid to avoid the enrollment of patients assuming other drugs potentially affecting cardiovascular adaptation to warm environments, we cannot exclude a possible role of concomitant medications in the observed hemodynamic responses.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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