Cardiovascular effects of eating, atenolol and their interaction: β_1 -adrenergic modulation does not play a predominant role in the genesis of postprandial effects

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- 1 Eight healthy subjects were investigated on four occasions at least 1 week apart when they either ate a standard 3100 kJ cold meal or fasted. One hour earlier, either 50 mg atenolol or placebo was administered.
- 2 Eating was followed by prominent changes of systolic cardiovascular function: a rise of heart rate (+7, 95% CI: 4 to 9 beats min^{-1}), systolic BP (+5, CI: 1 to 8 mmHg), a drop of diastolic BP (–6, CI: –9 to –3 mmHg), shortening of the pre-ejection period PEP (–11, CI: –13 to –9 ms) and electromechanical systole QS_2c (–13, CI: –17 to –8 ms), a rise of the estimated cardiac output CO (+1.3, CI: 1.0 to 1.6 l min^{-1}) and a reduction of the calculated total peripheral resistance TPR (–306, CI: –389 to –222 dyn s cm^{-5}).
- 3 Eating was also followed by an increase of the non-renal clearance of sorbitol (as a measure of hepatic blood flow) and this change was larger than proportional to the increase of CO. The plasma renin activity rose after the meal but the venous plasma noradrenaline and adrenaline concentrations were not affected.
- 4 The postprandial effects peaked over the first 1–2 h after the meal but remained well detectable up to 4 h after eating.
- 5 The administration of 50 mg atenolol before the meal reduced the postprandial effects to the same extent as the atenolol effects in the fasting state. This lack of interaction (or mere arithmetic additivity) indicates that the efferent β_1 -adrenergic tone does not play a predominant role in the modulation of postprandial cardiovascular changes.

Keywords eating food atenolol impedance cardiography sorbitol clearance catecholamines plasma renin activity

Introduction

Eating is known to induce substantial cardiovascular changes in normal man and patients with cardiovascular disease [1–7]: a rise of heart rate, an increase of systolic cardiac pump performance and a reduction of peripheral vascular resistance in particular. These chronotropic inodilatory responses [8] are associated with a rise of hepatic blood flow secondary to a rise of mesenteric blood flow. However there are few studies that assessed whether the postprandial rise of hepatic blood flow is larger than proportional to the rise of cardiac output. Furthermore there is little information on the contribution of adrenergic baroreflexes to the modulation of these postprandial changes. Preliminary observations indicated that a single oral dose of 50 mg atenolol indeed blunted the cardiovascular effects of eating but the chosen study design did not permit the analysis

of the nature and extent of the interaction [11]. The present study was carried out to assess the overall postprandial changes of cardiovascular function simultaneously with the changes of hepatic blood flow with and without β -adrenoceptor blockade.

Methods

Subjects

Eight male subjects (23 to 32 years of age, 63 to 88 kg body weight) who on the basis of extensive medical and laboratory investigations were judged to be healthy, participated in this study. The study was conducted

in agreement with the Declaration of Helsinki. The protocol was approved by an independent ethics committee. The subjects confirmed their consent to enrolment after detailed information had been provided.

Study design

Each subject was studied on four occasions at least 1 week apart when he received either a single oral dose of 50 mg atenolol (A) or matched placebo (P) followed 1 h later by 15 min upright sitting either eating (E) or fasting (F). The four treatments (PF, PE, AF, AE) were randomly allocated in a period-balanced within-subject 4-way crossover fashion. The subjects and observers were blinded for the nature of the medications.

Materials

Tablets of 50 mg atenolol (Batch B.ADM.51227/83) and matched placebo (B.ADM.57114/85) provided by ICI-Pharmaceuticals Division, Macclesfield, UK were used. Commercially available sorbitol solutions for intravenous infusion (Sorbit 40 Braun®, Melsungen, Germany) were used for the assessment of non-renal sorbitol clearance.

General study directives and restrictions

The subjects were studied after an overnight fast since 22.00 h. They stayed in bed in a relaxed recumbent position throughout the investigations. They abstained from any medication from 1 week before the first study day until the end of the study and they received dietary instructions for 2 days before each profiling day in order to avoid excessive sodium and potassium intake.

General study procedures

The subjects reported to the study room at 07.30 h. They emptied their bladder prior to the start of the observations. An i.v.-cannula was placed in a forearm vein of the right arm for venous blood sampling. A further i.v.-cannula was placed in a forearm vein of the left arm for the i.v.-infusion of sorbitol. Electrodes for one-lead ECG monitoring, a microphone for phonocardiographic (PCG) registration and electrodes for impedance cardiographic monitoring (ZCG) were positioned. A cuff for blood pressure measurement was placed around the right upper arm; the microphone incorporated in the cuff was positioned at the level of the maximum auscultatory sound of the brachial artery. Subsequently, clock time was set as $t = 0:00$, and an i.v.-infusion of 50 mg min^{-1} D-sorbitol (100 ml h^{-1} using an Infusomat II® pump, Braun, Melsungen, Germany) was started. After 3 h the subjects left the bed briefly in order to void urine. Twenty minutes later (time 3:20) placebo (treatments PF and PE) or 50 mg atenolol (treatments AF and AE) were administered. One hour later (time 4:20), the subjects sat upright in bed for 15 min, either reading (treatments PF and AF) or eating a standard meal (1 boiled egg, 2 bread rolls, 3 teaspoons margarine, 40 g ham, 40 g cheese and 230 ml orange juice; circa 3100 kJ representing approximately 19% protein, 39% fat, and 42% carbohydrates,

1.2 g sodium, 0.76 g potassium and 0.45 g calcium) as used in our previous studies [8, 11, 12]. Subsequently, the subjects resumed the supine position which they maintained for a further 4 h (up to time 8:35) under continuous infusion of sorbitol. During the profiling the subjects received the following amounts of fluid: approximately 860 ml by i.v.-infusion, 200 ml water orally with the medications, and 230 ml orange juice with the meal (eating subjects) or 230 ml water instead of the orange juice (fasting subjects).

Timing of investigations

Atenolol or placebo were administered at time 3:20. Eating or fasting (in sitting position) was timed from 4:20 to 4:35 h. Detailed cardiovascular measurements were carried out every 10 min throughout the investigation, up to 8:35 h after the start of the sorbitol infusion. Blood for the determination of plasma sorbitol concentrations was sampled before the start of the sorbitol infusion, times 0:30, 1:00, 1:30, 2:00, 2:30, 3:00, 3:40, 4:00, 4:20, 4:35 and then every 20 min up to time 6:35 and subsequently every 30 min up to 8:35 h. Plasma samples for the analysis of venous plasma catecholamine concentrations and plasma renin activity (PRA) were taken before dosing (time 3:15), before upright sitting – eating or not – (time 4:15), after 15 min upright sitting (time 4:35) and then every subsequent h (times 5:35, 6:35, 7:35, 8:35). Urine for the analysis of the renal sorbitol clearance was collected from time 0:00 to 3:00 and from 3:00 to 8:35 h.

Cardiovascular profiling

At each of the profiling time points specified above, the following variables were measured or calculated:

- HR (beats min^{-1}): heart rate from the ECG-recordings,
- SBP/DBP (mm Hg): systolic and diastolic blood pressure by graphical analysis of the sounds generated by the vascular wall motions [11]; this permits to evaluate DBP-equivalents of Korotkoff IV,
- STI (ms): systolic time intervals derived from ECG, ZCG and PCG; PEP (pre-ejection period), VETc (HR-corrected ventricular ejection time [13]) and QS_{2c} (HR-corrected total electromechanical systole),
- SV (ml): estimated stroke volume derived by ZCG according to Kubicek's equation [14],
- CO (l min^{-1}): estimate of cardiac output ($=\text{HR} \times \text{SV}/1000$),
- TPR (dyn s cm^{-5}): total peripheral resistance calculated the estimated CO and from mean blood pressure ($\text{MBP}=\text{DBP}+(\text{SBP}-\text{DBP})/3$; $\text{TPR}=80 \times \text{MBP}/\text{CO}$),
- HI ($\Omega \cdot \text{s}^{-2}$): impedance cardiographic Heather-index [15] of contractile performance.

Estimates of hepatic blood flow

Hepatic blood flow (EHBF) was calculated from the non-renal clearance (CL_{nr} ; $\text{EHBF}=\text{CL}_{\text{nr}}/(1-\text{Ht})$; Ht: haematocrit) of continuously infused sorbitol [17]. The investigational manoeuvres took place once stable steady state sorbitol concentrations had been reached.

Subsequent changes of the CL_{nr} (= total clearance CL_t minus renal clearance CL_r) with an unchanged infusion rate (50 mg min⁻¹) reflect changes of EHBF. Urine and plasma samples were frozen at -70°C immediately after collection and subsequently assayed via photometric analysis of NADH, the co-substrate for the enzymatic conversion of sorbitol to fructose [18].

Catecholamines and plasma renin activity

The venous plasma concentrations of noradrenaline and adrenaline (sampled in ice-chilled tubes with sodium metabisulphite) were assayed by h.p.l.c. with electrochemical detection [19]. PRA was assayed with a standard commercial RIA-kit (REN CTK, Sorin, Biomedica, Italy). The lower limits of quantitation were: 0.296 nM, 0.027 nM for noradrenaline and adrenaline and 0.22 ng ml⁻¹ h⁻¹ for PRA, respectively.

Data analysis

The supine resting cardiovascular data were summarised for representative time zones: TZ(0:00–2:00) and TZ(2:00–3:00) before dosing, TZ(3:20–3:50) and TZ(3:50–4:20) after dosing and before eating, TZ(4:45–5:35), TZ(5:35–6:35), TZ(6:35–7:35) and TZ(7:35–8:35) after eating.

For each time zone the area-weighted average value was calculated, as the area under the time course of the data divided by the duration of the respective time segment. The post-dosing data were then Δ -transformed as arithmetic differences from the pre-dosing baseline (TZ(2:00–3:00)).

These Δ -values were fitted to a general linear model with effects for subjects (1,...,8), periods (1,...,4) and treatment (PF, PE, AF, AE).

The residual variance was used to calculate the 95% CI intervals of the treatment differences (PE, AF and AE) vs PF (according to Dunnett [20]).

The three treatment related degrees of freedom were furthermore partitioned to analyse the following three linear treatment contrasts: the overall effect of atenolol [A vs. P: ((AF-PF)+(AE-PE))/2], the overall effect of eating [E vs. F: ((PE-PF)+(AE-AF))/2] and their interaction [ExA: (PE-PF-AE+AF)/2] for which a point estimate and the corresponding 95% CI were calculated

[21]. The interaction component permits to assess whether the effects were additive but does not locate the direction of non-additivity.

A similar analysis of overall effects and interaction was carried out for the supine plasma catecholamines and PRA (Δ -transformed from the data at time 3:15), sitting catecholamines and PRA at time 4:35 (Δ -transformed from the sitting values at time 4:20) and for the clearance data of sorbitol (untransformed).

Results

Overall cardiovascular effects

Eating caused an overall rise of HR, a rise of SBP, a drop of DBP (Figure 1) and MBP, a shortening of PEP, VET_c and QS_{2c} (Figure 2), a rise of the estimated SV and CO, a drop of the average TPR (Figure 3) and a rise of the indices of systolic contractile performance. A single dose of 50 mg atenolol administered 1:30 h earlier induced an overall drop of HR and SBP, a prolongation of PEP, an HR-dependent drop of CO, a rise of estimated TPR and a reduction of the ZCG-indices of contractile performance. There was no statistically significant interaction between these effects, i.e. the effects of atenolol and eating were merely additive. Atenolol did not blunt the postprandial cardiovascular effects to a larger extent than its effects in the resting supine non stimulated state.

Sorbitol clearance

The time course of the median plasma sorbitol concentrations is presented in Figure 4 (constant infusion rate of 50 mg min⁻¹). The corresponding estimates of the CL_t, CL_r and CL_{nr} of plasma sorbitol are summarised in Table 1. Eating thus caused a drop of the plasma concentrations of sorbitol in spite of the unchanged infusion rate. The rise of the CL_t is solely accounted for by an increase of the CL_{nr}. Atenolol in contrast caused a rise of the plasma concentrations of sorbitol and a drop of CL_t and CL_{nr}. The effects of atenolol and eating were merely additive. Across the treatments, the changes of the CL_{nr} over the first h after sitting upright (eating or not) were closely related with

Table 1 Mean total, renal and non-renal sorbitol plasma clearance before dosing and after dosing for each treatment (PF: placebo+fasting, PE: placebo+eating, AF: atenolol+fasting and AE: atenolol+eating) plus the corresponding point and interval estimates (95% CI) of the overall effects of a single dose of 50 mg atenolol (A vs P), of eating (E vs F) and their interaction (NS: statistically not significant at α : 0.05; *: statistically significant).

Variable	Mean (PF)	Mean (PE)	Mean (AF)	Mean (AE)	[A vs P]	(95% CI)	[E vs F]	(95% CI)	Interaction
<i>CL_t: total plasma sorbitol clearance (ml min⁻¹)</i>									
CL _t (2:00 to 3:00)	702	705	710	726	14	(-20, 49)	10	(-24, 44)	NS
CL _t (3:00 to 8:15)	683	881	604	773	-94	(-133, -54)*	184	(144, 223)	NS
<i>CL_r: renal plasma sorbitol clearance (ml min⁻¹)</i>									
CL _r (2:00 to 3:00)	102	104	103	103	0	(-5, 5)	1	(-4, 6)	NS
CL _r (3:00 to 8:15)	102	104	100	106	0	(-7, 8)	4	(-4, 11)	NS
<i>CL_{nr}: non-renal plasma sorbitol clearance (ml min⁻¹)</i>									
CL _{nr} (2:00 to 3:00)	600	601	606	623	14	(-19, 47)	9	(-24, 42)	NS
CL _{nr} (3:00 to 8:15)	582	778	504	668	-94	(-131, -56)*	180	(142, 217)*	NS

Figure 1 Treatment contrasts for heart rate (HR, beats min^{-1}), systolic (SBP, mmHg) and diastolic blood pressure (Korotkoff IV, DBP, mmHg). Left panels: time course of the mean changes from pre-dosing baseline for treatment PF (○: placebo+fasting; the bars indicate the least significant differences of the active treatments vs. PF, $\alpha:0.05$, according to Dunnett), treatments PE (△: placebo+eating), AF (▽: atenolol+fasting) and AE (◇: atenolol+eating). Right panels; time course of overall effects (+95% CI) of eating (▼: E), atenolol (▲: A) and their interaction (◆: ExA).

the change of CO (Figure 5) but involved CO-independent (i.e. vascular) changes as well (Figure 6).

Venous plasma catecholamines and PRA

The plasma concentrations of noradrenaline (NOR) and adrenaline (ADR) and the plasma renin activity (PRA) at the various time points and their contrasts are summarised in Table 2. The administration of atenolol was rapidly followed by a rise of plasma NOR and a quite pronounced drop of PRA. Sitting upright (time 4:35 relative to time 4:20) caused a rise of NOR which was amplified by both eating and atenolol. Eating immediately caused a rise of PRA which peaked at 2 h after the meal. Eating in contrast hardly affected supine NOR but tended to decrease supine ADR.

Miscellaneous observations

The urinary volume excreted from time 3:00 to 8:35 was about 1/3 lower for the eating treatments : the

corresponding overall effect was -352 ml (95% CI: -497 to -208). The urinary excretion of Na^+ , K^+ and creatinine and the Na^+ /creatinine-ratio were not altered though. Eating was followed by a rise of serum Na^+ ($+4.3$, 95% CI: 1.8 to 6.8 mEq l^{-1}) but serum creatinine remained unaffected. Serum potassium in contrast was slightly reduced (-0.2 , 95% CI: -0.3 to -0.0) after eating.

Discussion

Eating is generally known to cause substantial cardiovascular changes, mainly characterised by a rise of heart rate and cardiac output and a reduction of the systemic vascular resistance. The present findings are in agreement with such a chronotropic inodilatory profile. The present observations also document a substantial drop of diastolic blood pressure and a small rise of systolic blood pressure which confirms previous findings under

Figure 2 Treatment contrasts for the pre-ejection period (PEP, ms), ventricular ejection time (VETc, ms) and total electro-mechanical systole (QS_{2c}, ms). Left panels: time course of the mean changes from pre-dosing baseline for treatment PF (○: placebo+fasting; the bars indicate the least significant differences of the active treatments vs PF, α :0.05, according to Dunnett), treatments PE (△: placebo+eating), AF (▽: atenolol+fasting) and AE (◇: atenolol+eating). Right panels; time course of overall effects (+95% CI) of eating (▼: E), atenolol (▲: A) and their interaction (◆: ExA).

identical circumstances [8, 11, 12] and some reports by others [5, 6] but does not seem to be a general trend. Elderly patients, especially when frail, usually show a reduction of systolic blood pressure as well [22, 23]. The differences between the various studies (especially with regard to postprandial blood pressure changes) may relate to the many other variables involved: the nature of the meal (often not well defined), its size, energy content and composition [1, 24, 25], its constitution, temperature, palatability [26], whether coffee was permitted [27, 28], etc., the study population (normals or patients) and the nature of the study (whether a control treatment was used or not). The discrepancies with regard to blood pressure changes are also related to the methods used. Invasive data in normals and hypertensives [29], post-infarction patients [7], patients with diagnostic catheterisation [30, 31] or patients with congestive heart failure [2, 32] usually reported systolic and mean pressure only and if reported, showed little if any reduction of diastolic blood pressure. Auscultatory methods based on Korotkoff V endpoints in contrast are

exceptionally sensitive to inodilatory changes and thus yield inflated estimates of the postprandial drop of systemic vascular resistance and diastolic blood pressure. This can be reduced (as shown here also) by using observer independent Korotkoff IV equivalents derived by graphical analysis of the vascular sound signals [29, 33]. The findings of the present study, although method-specific, suggest resetting of the pressure homeostasis after eating as the (vasoconstrictive) baroreflexes fail to counter the primary vasodilatory changes.

Eating furthermore caused pronounced changes of the systolic time intervals suggestive of both cardiac and vascular prandial effects. It should be noted that the impact of changing HR on the electromechanical systole (QS₂) is not optimally accounted for by Weissler's equation [13]. Alternative corrections for HR [34] were considered (data on file) which did not change the present conclusions. Weissler's format is reported here in order to maintain consistency with our previous reports.

Postprandial vasodilatation included the hepatic/

Figure 3 Treatment contrasts for the estimated stroke volume (SV, ml), cardiac output (CO, l min⁻¹) and total peripheral resistance (TPR, dyn s cm⁻⁵). Left panels: time course of the mean changes from pre-dosing baseline for treatment PF (○: placebo+fasting; the bars indicate the least significant differences of the active treatments vs PF, $\alpha:0.05$, according to Dunnett), treatments PE (△: placebo+eating), AF (▽: atenolol+fasting) and AE (◇: atenolol+eating). Right panels; time course of overall effects (+95% CI) of eating (▼: E), atenolol (▲: A) and their interaction (◆: ExA).

Figure 4 Time course of the mean plasma sorbitol concentrations before and after dosing of atenolol or placebo (time 3:30) and upright sitting (eating or not, time: 4:20 to 4:35) for treatments PF: placebo+fasting (○), PE: placebo+eating (▽), AF: atenolol+fasting (△) and AE: atenolol+eating (◇).

Figure 5 Relationship between the change of non renal sorbitol clearance and cardiac output over the first postprandial hour (PF: placebo+fasting (○), PE: placebo+eating (▽), AF: atenolol+fasting (△) and AE: atenolol+eating (◇)).

Table 2 Mean venous plasma noradrenaline and adrenaline concentrations and PRA before dosing (3:15), during upright sitting – eating or not – (4:35) and during the further profiling for each of the 4 treatments (PF: placebo+fasting, PE: placebo+eating, AF: atenolol+fasting and AE: atenolol+eating) plus the corresponding point and interval estimates (95% CI) of the overall effects of a single dose of 50 mg atenolol (A vs P), of eating (E vs F) and their interaction (NS: statistically not significant at α : 0.05; *, statistically significant). The supine resting data after dosing were transformed as differences from the baseline value before dosing. The postural data were transformed as difference from the supine data immediately before upright sitting.

Variable	Mean (PF)	Mean (PE)	Mean (AF)	Mean (AE)	[A vs P]	(95% CI)	[E vs F]	(95% CI)	Interaction
<i>Plasma noradrenaline (nmol l⁻¹)</i>									
C(3:15)	0.73	0.80	0.77	0.80	0.02	(-0.08, 0.12)	0.05	(-0.05, 0.15)	NS
C(4:20)-C(3:15)	0.04	0.00	0.16	0.20	0.16	(0.04, 0.27)*	0.00	(-0.11, 0.12)	NS
C(4:35)-C(4:20)	0.31	0.58	0.72	1.00	0.42	(0.26, 0.57)*	0.27	(0.12, 0.43)*	NS
C(5:35)-C(3:15)	0.02	0.14	0.27	0.42	0.27	(0.12, 0.42)*	0.14	(-0.01, 0.29)	NS
C(6:35)-C(3:15)	0.01	0.05	0.23	0.36	0.32	(0.15, 0.48)*	0.03	(-0.13, 0.20)	NS
<i>Plasma adrenaline (nmol l⁻¹)</i>									
C(3:15)	0.10	0.11	0.12	0.13	0.02	(-0.01, 0.05)	0.01	(-0.02, 0.04)	NS
C(4:20)-C(3:15)	-0.00	0.02	-0.00	0.04	0.01	(-0.01, 0.03)	0.03	(0.01, 0.05)*	NS
C(4:35)-C(4:20)	0.04	-0.00	0.09	0.04	0.04	(0.01, 0.08)*	-0.05	(-0.08, -0.01)*	NS
C(5:35)-C(3:15)	0.03	-0.00	0.02	-0.04	-0.02	(-0.07, 0.02)	-0.04	(-0.09, 0.00)	NS
C(6:35)-C(3:15)	0.03	-0.02	0.06	-0.01	0.02	(-0.02, 0.06)	-0.06	(-0.10, -0.02)*	NS
<i>Plasma renin activity (ng ml⁻¹ h⁻¹)</i>									
C(3:15)	1.26	1.23	1.49	1.48	0.23	(-0.05, 0.52)	-0.02	(-0.31, 0.27)	NS
C(4:20)-C(3:15)	0.31	-0.02	-0.54	-0.58	-0.71	(-0.98, -0.44)*	-0.18	(-0.45, 0.09)	NS
C(4:35)-C(4:20)	-0.00	0.35	-0.02	0.08	-0.14	(-0.29, 0.01)	0.22	(0.07, 0.37)*	NS
C(5:35)-C(3:15)	0.01	1.87	-0.69	0.70	-0.93	(-1.29, -0.58)*	1.63	(1.27, 1.98)*	NS
C(6:35)-C(3:15)	0.12	0.70	-0.61	-0.31	-0.87	(-1.18, -0.56)*	0.44	(0.14, 0.75)*	NS

Figure 6 Changes of the estimated hepatic blood flow during the first hour after sitting upright (eating or not) relative to baseline values before the administration of atenolol or placebo for treatments PF (placebo+fasting), PE (placebo+eating), AF (atenolol+fasting) and AE (atenolol+eating). The cross-hatched area is the change that would correspond with the change of cardiac output (i.e. with unchanged EHBF/CO-ratio).

mesenteric vascular bed, as was expected, but, a large proportion of the rise in hepatic blood flow was explained solely by the rise of cardiac output. This emphasises the need to investigate cardiac function simultaneously.

There was no rise of venous plasma noradrenaline and adrenaline in spite of the dramatic cardiovascular changes. This agrees with previous findings under identical [8, 11, 35] and different circumstances [36, 37] but does not agree with the rises of venous plasma noradrenaline [38, 39] or adrenaline [40] reported by others. Venous plasma catecholamine concentrations are notoriously rough estimates of the efferent (nor)-adrenergic tone [41, 42], albeit that they were sensitive enough to detect postural increases of catecholamines

during eating and their amplification by atenolol in the present study. In the present case, the absence of a postprandial rise of venous catecholamines might be the net result of an enhanced efferent release countered by inodilatory amplification of peripheral disposition [36]. Changes of peripheral disposition, well documented for propranolol [43], might also explain the observed rise of noradrenaline caused by atenolol.

Eating was followed by a rather large increase of PRA, which agrees with our previous findings [8, 11, 34] and those reported by others [44]. This rise was blunted but not inhibited by atenolol (see below) and thus is more likely to relate to non- β_1 -adrenergic postprandial mechanisms [45, 46]. There was a slight postprandial rise of serum Na^+ , as also reported by others [47], but no evident aldosterone effect (urinary K^+ -excretion was not increased). This might relate to a postprandial enhancement of aldosterone clearance [48]. There nevertheless was a small and rapidly transient drop of serum K^+ which might be insulin-dependent of origin [49]. This might contribute to the postprandial electrocardiographic repolarisation changes that have been reported in specific subjects [50].

A single oral dose of 50 mg atenolol had clearly detectable albeit smaller effects on the cardiovascular system. Atenolol was chosen in the present context because of its lack of partial agonistic effects [51], the relatively low variability of its plasma concentrations [52], its relatively weak metabolic effects [53, 54] and its relatively high β_1 -adrenoceptor selectivity at the present dose [55–57]. Atenolol's effects were opposed to those of eating but their combination was merely additive, i.e. the administration of atenolol blunted the subsequent postprandial effects but only to the extent of its intrinsic effects in the non stimulated (fasting) condition. This lack of inhibition by atenolol for virtually all aspects of the profiling indicates that β_1 -adrenergic

modulation did not play a predominant role in the genesis of the observed postprandial cardiovascular changes. The role of the autonomic nervous system (and its integrity) might be important in patients, as autonomic dysfunction promotes symptomatic postprandial dysfunction [58] and this is aggravated by propranolol [59].

The primary mediators of the cardiovascular changes are likely to be directly related to the digestive process. Extrinsic and intrinsic nerves indeed only play a minor role in nutrient-induced hyperaemia which in essence appears to be a local process [60–62]. But, the vasodilatory responses to eating are not confined to the mesenteric (i.e. digestive) tract. Indeed, protein-rich meals in particular have been shown to increase renal blood flow and glomerular filtration [63, 64] with changes proportional to protein load and likely to be larger than merely expected on the basis of the increased cardiac output. The complexity and multiplicity of the mechanism of postprandial cardiovascular

changes is best demonstrated by the observation that only somatostatin analogues were reported to cause a dramatic improvement of postprandial symptomatic hypotension in autonomic dysfunction [65].

This suggests that the postprandial cardiovascular changes are likely to be far more complex than the simplified scenario of primary digestive hyperaemia with secondary baroreflex mediated cardiovascular (compensatory changes). The various postprandial systemic and local cardiovascular changes that were detailed above thus must be seen as the net effects of several interrelated effector drives many of which might be opposed by others that are either activated simultaneously or in secondary fashion as a compensatory response. Our findings indicate that β_1 -adrenergic modulation does not play a predominant role in this regard.

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