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ORIGINAL CONTRIBUTION

M. Brändle
S. Al Makdessi
R. K. Weber
K. Dietz
R. Jacob

Prolongation of life span in hypertensive rats by dietary interventions. Effects of garlic and linseed oil

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M. Brändle · S. Al Makdessi
Prof. Dr. R. Jacob (✉)
Physiologisches Institut, Abteilung II
Universität Tübingen
Gmelinstraße 5
72076 Tübingen, Germany

R. K. Weber
Pathologisches Institut
Universität Tübingen
Gmelinstraße 5
72076 Tübingen, Germany

K. Dietz
Institut für Medizinische Biometrie
Universität Tübingen
Gmelinstraße 5
72076 Tübingen, Germany

Abstract The effects of long-term dietary application of garlic (dried powder, 0.5 % in weight of standard chow; G group) or linseed oil (2.5 %; L group) as well as a combination of both interventions (L+G group) on the life span of hypertensive rats (SHR SP) was investigated. A further group fed with standard chow served as control (C). The dietary interventions were started at the age of three weeks. Besides regular measurements of the systolic arterial blood pressure (oscillometrically at the tail artery) as well as of heart rate and body weight, autopsy and histological investigations were performed.

Both diets, and particularly their combination, prolonged life span significantly (mean values (days) C: 434.5 ± 23.5; G: 453.2 ± 16.2; L: 470.0 ± 26.2; L+G: 494.8 ± 39.2).

There was no significant interaction of the factors garlic and linseed oil. Systolic blood pressure as measured during the compensatory stage (data used until the 39th week of life) was significantly lowered by both garlic (mean −5.8 mm Hg), linseed oil (mean −6.3 mm Hg), and their combination (mean −11.3 mm Hg).

The animals died as a consequence of congestive left and right ventricular failure with ventricular hypertrophy, dilatation, myocardial fibrosis and cellular infiltration, left ventricular atrial thrombosis (in most cases), and terminal pneumonia. On the other hand, arteriosclerotic plaques and signs of cerebral stroke could not be detected. Except for the degree of hypertrophy, which was lower in the treated groups, no differences were obvious regarding the morphological findings at the time of death. There was a significant positive correlation between mean blood pressure and the degree of left ventricular hypertrophy. Furthermore, a significant negative correlation between mean blood pressure and ventricular hypertrophy on the one hand and survival on the other hand was obvious provided the total number of animals was considered, however, not within the individual groups. The same applies to the relation between the reduction of left ventricular hypertrophy and life span.

The relatively slight hypotensive effect of both dietary interventions as well as the results of previous investigations speaks in favor of a substantial influence of factors independent of blood pressure. In view of controversial results and interpretations in international literature, the mechanisms involved need further study.

Key words Hypertensive rats – life span – garlic – linseed oil – blood pressure – cardioprotection

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Introduction

Chronic arterial hypertension reduces life span due to secondary cardiovascular damage and consecutive impairment of vital organs. Therapeutic and prophylactic interventions predominantly aim at lowering blood pressure. However, additional protective measures on the organ and cellular level should be taken into account also in chronic diseases. A large number of reports in literature (see discussion) as well as previous investigations of our own group indicate that in this context dietary interventions may be relevant. Diets enriched with polyunsaturated fatty acids (PUFAs), particularly of the n-3 type, resulted in beneficial effects on blood pressure, rheologic parameters, and plasma lipids and exerted cardioprotective actions under the conditions of ischemia and reperfusion (3, 5, 8, 14, 15, 17, 19, 34). Similar actions were found after long-term administration of garlic (14, 16, 18, 19, 33, 44). Thus, the question arises whether and to what extent dietary interventions alone are able to prolonge the life span of hypertensive individuals.

It was the aim of the present study to investigate the influence of garlic and of a vegetable oil rich in n-3 fatty acids on life span in hypertensive rats. For this purpose, garlic powder with standardized alliin content or linseed oil was added to a standard chow in a relatively small dosage. In addition, we applied a combination of both interventions in another group, particularly considering the radical scavenger properties of garlic that could compensate conceivable unfavourable side effects of PUFAs.

Material and methods

Forty male stroke prone rats (SHR SP, SAVO Invanovas, Kisslegg/FRG) at the age of three weeks were randomly divided into four groups of equal size. The control group (C) was fed a standard chow (Ssniff) containing 50 % carbohydrate, 21 % protein, 3 % fat, 4.8 % crude fiber (data by Ssniff). Fatty acid composition of the standard chow as analysed by gas chromatography was 14:0, 1.8 %; 16:0, 18.9 %; 18:0, 4.4 %; 18:1 (n-9), 21.3 %; 18:1 (n-7), 0.5 %; 18:2 (n-6) 48.4 %; 18:3 (n-3), 2.8 %. The other groups received 0.5 % dried garlic powder (G) or 2.5 % linseed oil (L), respectively, or a combination of G+L added to the standard food.

The garlic powder used (corresponding to Kwai®/ Sapec®) was prepared immediately after harvesting the garlic cloves by careful air drying. This powder is characterized by a very high content of sulphur-containing components and standardized to an alliin content of 1.3 % and a capacity for liberation of allicin of 0.6 % (46). The fatty acid composition of linseed oil used in oil study is 16:0, 7.4 %; 18:0, 2.0 %; 18:1 (n-9), 15.9 %; 18:1 (n-7), 0.7 %; 18:2 (n-6), 20.7 %; 18:3 (n-3), 53.3 %. Starting at the age of three weeks, all diets were administered without interruption until the time of death. The rats were housed in a room maintained at 21–23 °C and kept on a 12-h light-dark cycle. Food and water were *ad libitum*. Freshly prepared food was supplied every three days.

Blood pressure was measured on the tail artery between 9.00 and 11.0 p.m. using a piezzoelectric pressure transducer. The first measurement was possible at the age of 6 weeks. Systolic blood pressure, heart rate, and body weight were determined on the average 1.4 times per week. ECG was recorded at the final stage, particularly in consideration of the occurrence of atrial fibrillation.

There were only minor differences between the various groups with regard to the initial values of body weight (mean values at the age three-week-stage: C: 63 g; G: 60 g; L: 65 g; G+L: 62 g). Systolic blood pressure, which is difficult to measure in small animals, at the six-week-stage was C: 151 ± 17 mmHg; G: 153 ± 15 mmHg; L: 147 ± 12 mmHg; G+L: 147 ± 13 mmHg.

After the death of the animals, an autopsy was performed with particular regard to the following data: occurrence of skin edema, pleural effusion and ascites, left and right ventricular weight. Furthermore, we were interested in detection of arteriosclerotic plaques in the aorta and the large arterial vessels, arterial intima and media hyperplasia, atrial thrombosis, and cerebral stroke. Cardiac hypertrophy was assessed by the ventricular weight/body weight ratio and the ventricular weight/tibia length ratio. Histological investigations were performed on heart, lung, liver, kidney, and brain. Collagen concentration was estimated using hydroxyproline determination (24).

The experimental procedures were approved by the Committee for Animal Care and Use of the University of Tübingen.

Statistics

For the statistical analysis of the data we used linear regression and analysis of variance for factorial designs. The calculations were performed by the statistical package JMP (20). Since none of the interaction terms were significantly different from zero, the effects in the group treated with garlic and linseed oil combined (G+L) are given by the sum of the individual effects of garlic and linseed oil as estimated from the complete data set. All data are expressed as mean ± standard deviation (except for body weight, when determined for several animals together).

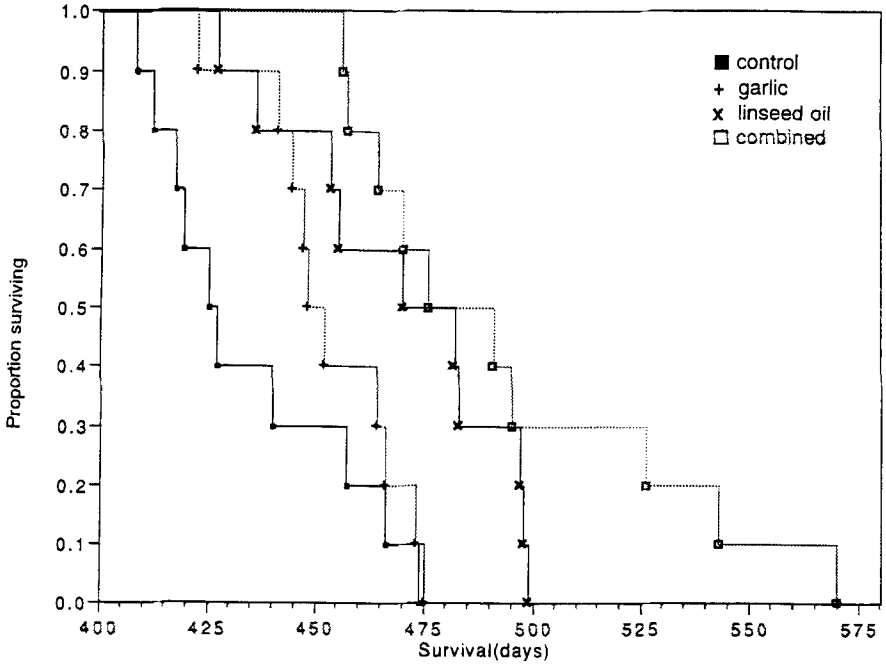

Fig. 1 Survival of the four groups of hypertensive rats.

Results

Life span

In the four groups of stroke prone rats investigated, no symptoms of infections were observed during the period of observation with the exception of the last few days of life (see below). No signs of paralysis could be observed.

The first animal of the group C died at the age of 408 days, and 66 days later, all of the control group had died (Fig. 1). Mean life span in this group was 434.5 ± 23.5 days. In the G group, life span on the average was prolonged by 18.7 days to 453.2 ± 16.4 days. Linseed oil produced a mean prolongation of 35.5 days to 470.0 ± 26.2 days. There was no significant interaction of the factors garlic and linseed oil ($p = 0.73$). The individual comparison of the C group with the group G+L showed a prolongation of mean life span by 60.3 days ($p < 10^{-4}$) to 494.8 ± 39.2 days, i.e., 14 % of life time. Using the two-factorial analysis of variance model, the increase in survival by garlic was estimated at 21.8 days ($p < 0.02$) and by linseed oil at 38.6 days ($p < 0.0001$). Mean life span, calculated according to this model, was very close to the observed values: C = 432.9 days; G = 454.7 days; L = 471.5 days; G+L = 493.3 days.

Blood pressure and heart rate

Systolic blood pressure was ca. 150 mmHg at the 6-week-stage and increased to a maximum of 242 mmHg at the age of 14.5 months (group C) (Fig. 2). During the compensatory stage (data used until the 39th week of life), blood pressure was significantly lowered by both linseed oil (mean: −6.3 mmHg; $p < 0.001$) and garlic (mean: −5.0 mmHg; $p < 0.01$). This means that in the combined group the estimated reduction was about 11.3 mmHg.

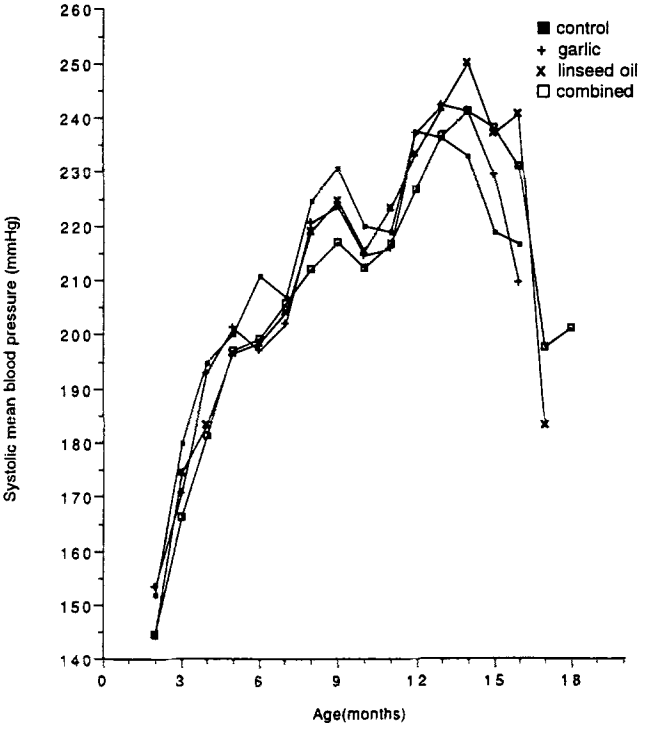

Fig. 2 Time course of systolic blood pressure during the period of observation (average values per month). Note the terminal decrease.

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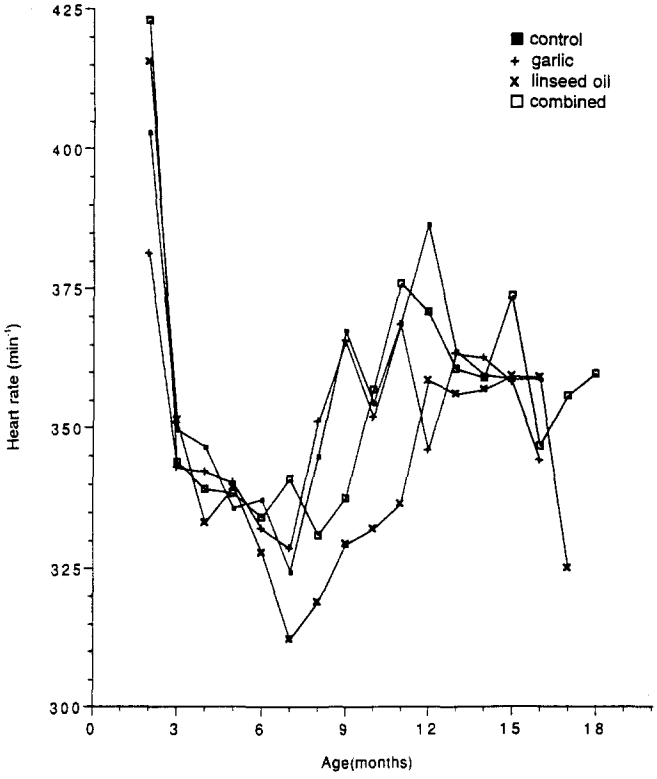

Fig. 3 Time course of heart rate during the period of observation (average values per month).

In the later stages, beginning at the 13th–14th month of life, the control curve fell below the other three curves indicating earlier manifestation of cardiac failure.

Heart rate showed considerable variations in all groups, the initial mean value being 405/min at the 6-week-stage. There was rapid decline during the following month (to a mean value of 347/min) and a slower decrease during the 7–8 month-stage (Fig. 3). A tendency towards bradycardia in the garlic group, which appears in the first measurement, would be consistent with previous results (9). No atrial fibrillation could be detected by ECG, which is noteworthy considering the high incidence of atrial thrombosis (see below).

Body weight and tibia length

There were only minor differences in body weight during the compensatory stage, e.g., mean values at the 28th week stage: C: 319 g; G: 315 g; L: 310 g; G+L: 314 g. In all groups, body weight increased until death and, thus, the final post-mortem values rather show an increasing tendency (n.s.) according to life span: C: 319 ± 63; G: 326 ± 58; L: 323 ± 47; G+L: 333 ± 49; (great scattering due to the variation in time of death). Tibia length of the animals as examined by post-mortem measurement did not differ significantly between the various groups (Table 1).

Ventricular weight and degree of hypertrophy, left ventricular collagen content

In all rats investigated, considerable left ventricular hypertrophy as well as dilatation of all cardiac chambers were present. The post-mortem data show a tendency towards reduced hypertrophy in the treated groups (Table 1). Mean left ventricular weight, but also right ventricular weight, were lower in the treated groups (C > G > L > G+L) although body weight exhibited a rather increasing tendency. A significant reduction of the left ventricular weight/body weight ratio by 13 % was found in the linseed oil group ($p < 0.035$). On the other hand, the group with the longest survival rate (G+L) showed the highest left ventricular collagen content per unit mass assessed on the basis of hydroxyproline determination (Table 1) (for comparison, the values of young Wistar rats is ~ 2.6 μg/mg). This means that myocardial fibrosis increased with life span.

Further post-mortem data

In most of the animals, histological examination of heart, lung, liver, kidney, and brain was performed (Table 2).

Table 1 Protocol of autopsy data. BW: body weight; Tib: tibia length; LVW: left ventricular weight; RVW: right ventricular weight; Hydrox: hydroxy-proline concentration; Thrombus: Incidence of parietal thrombi in the left atrium.

	Mean life span (days)	BW (g)	Tib (mm)	LVW (g)	LVW/Tib × 100 (g/mm × 100)	LVW/BW × 100 (%)	RVW (g)	RVW/Tib × 100 (g/mm × 100)	RVW/BW × 100 (%)	Hydrox (μg/mg)	Thrombus
C	434.5 ± 23.5	313 ± 63	41.5 ± 0.6	1.45 ± 0.28	3.49 ± 0.67	0.47 ± 0.09	0.42 ± 0.08	1.01 ± 0.21	0.14 ± 0.02	10.5 ± 1.6	9/10
G	453.2 ± 16.4	326 ± 58	41.9 ± 0.6	1.38 ± 0.15	3.30 ± 0.35	0.43 ± 0.07	0.41 ± 0.06	0.98 ± 0.15	0.13 ± 0.02	9.7 ± 2.0	9/10
L	470.0 ± 26.2	323 ± 47	41.8 ± 0.3	1.30 ± 0.19	3.11 ± 0.46	0.41 ± 0.07	0.39 ± 0.09	0.92 ± 0.22	0.12 ± 0.03	11.7 ± 2.0	5/10
G+L	494.8 ± 39.2	333 ± 49	41.2 ± 1.1	1.28 ± 0.17	3.10 ± 0.41	0.40 ± 0.05	0.38 ± 0.04	0.93 ± 0.08	0.12 ± 0.02	13.2 ± 1.9	10/10

Table 2 Histological examination of pathological alterations. Incidence of alterations related to the number of investigated specimen. Heart: Fibrosis and cellular infiltration. Vessels: Intima and media hyperplasia without necrosis or arteriosclerotic plaques. C = Control; G = Garlic group; L = Linseed oil group; L+G = Group with combined application of garlic and linseed oil.

	Heart			Lungs		Liver	Kidney	Brain
	Atrium	Left ventricle	Right ventricle	Pneumonia	Vessels	Acute congestion	Vessels	Stroke
C	4/4	4/4	4/4	1/4	4/4	3/3	4/4	0/4
G	6/7	7/7	7/7	5/6	6/6	3/3	6/6	0/4
L	7/8	7/8	7/8	8/8	8/8	6/6	6/7	0/6
L+G	9/10	10/10	10/10	8/10	10/10	7/7	10/10	0/7

Heart

Examination of right and left ventricular myocardium revealed a high degree of interstitial and perivascular fibrosis, cellular infiltration, and also focal necroses, particularly in the subendocardial layers, practically in all animals without obvious differences between the various groups. These alterations corresponded to the picture of myocarditis and were more pronounced in the left than in the right ventricle.

An interesting observation is the occurrence of parietal thrombosis in the left atrium. These partially organized thrombi were found in most animals of all groups; the L group showed the lowest incidence (Table 1). Despite their large size, no relation to the time of death was recognizable. Furthermore, in most animals signs of myocardial inflammation were also found in the subendocardial layers of the left atrium.

Arterial vessels

Ateriosclerotic plaques could not be detected in the aorta nor in large arterial vessels and coronary arteries in any of the 40 animals investigated. However, the small vessels of the coronary system revealed increased wall thickness due to intima and media hyperplasia without obvious differences between the four groups. Hypertrophy of smooth muscle cells was particularly pronounced in renal arteries.

Brain

Surprisingly, all brains investigated showed only slight alterations such as hyperemia due to congestion and small older necroses. Acute cerebral infarction or hemorrhage were not detectable.

Symptomes of congestion, ultimate cause of death

In most animals, histological examination revealed not only signs of congestion and edema, but also of inflammation of the lungs, indicating that terminal infection preceded death. With the exception of three animals, all specimens regardless of their respective group showed pleural effusion, ascites, and skin edema. Histological findings also indicate the presence of pulmonary hypertension. Furthermore, the typical picture of acute liver congestion was present, whereas ascites was found in only ca. 40 % of the animals without obvious differences between the various groups.

The animals died as a consequence of combined left and right pumping failure, which in most cases was accompanied and intensified by terminal pneumonia.

Correlations

A significant negative correlation was observed between life span and systolic arterial blood pressure during the period of compensation (calculated until the 39th week) taking into account the total number of animals used in the study (n = 40). However, dependence of survival on blood pressure cannot be statistically demonstrated within the individual groups (Fig. 4).

The same applies to the correlation between survival and degree of left ventricular hypertrophy (expressed as left ventricular weight/body weight ratio) (Fig. 5). A significant negative correlation occurs if all animals are considered, however, not within the various groups. Left ventricular weight related to tibia length shows the same tendency.

As could be expected, a significant positive correlation can be shown between left ventricular weight and degree of hypertrophy on the one hand (not shown) and systolic

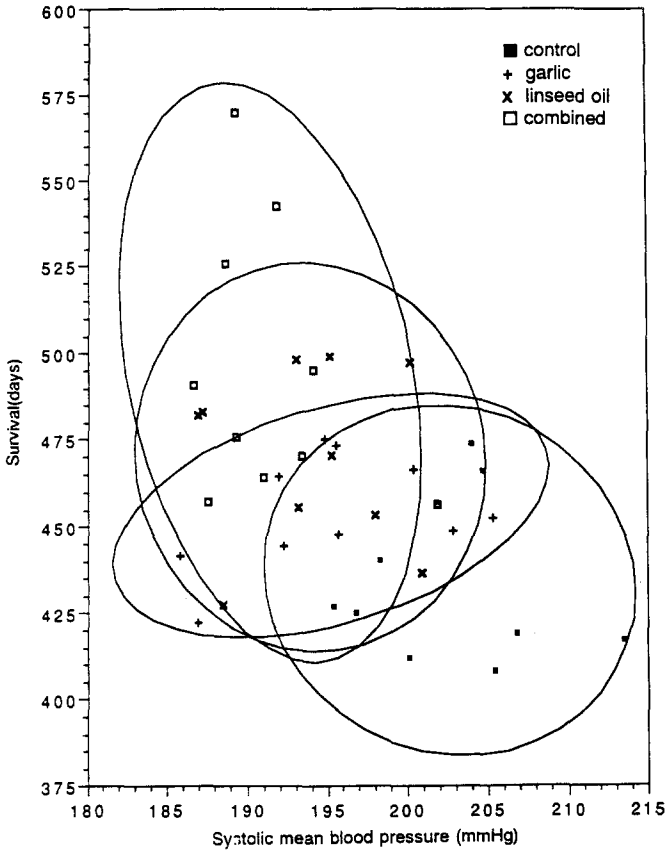

Fig. 4 Life span as a function of mean systolic arterial pressure as measured until the 39th week of life). A bivariate normal distribution is adapted by an ellipse for each group, containing 90 % of the individual values.
Control group: r = −0.074; p = 0.84. Garlic group: r = 0.404; p = 0.25. Linseed oil group: r = −0.042; p = 0.91. Combined group: r = −0.300; p = 0.40. All data: r = −0.404; p = 0.01.

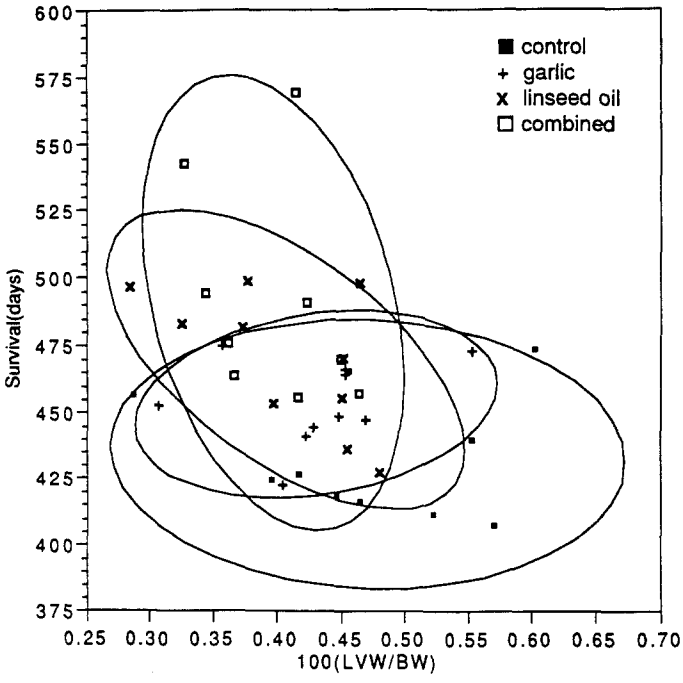

Fig. 5 Life span as related to the left ventricular weight/body weight ratio.
Control group: r = −0.057; p = 0.88. Garlic group: r = 0.225; p = 0.53. Linseed oil group: r = −0.602; p = 0.07. Combined group: r = −0.337; p = 0.38. All data: r = −0.374; p = 0.02.

arterial pressure on the other (Fig. 6). Furthermore, body weight increased with life span ($p < 0.05$); a survival of 10 days corresponded to an increase in body weight by 4.7 g.

Discussion

The protective effect

The present study gives evidence that the life span of hypertensive rats can be considerably prolonged by dietary interventions. In this respect, particularly the comparably low dosage of the agents we applied in our long-term experiment should be emphasized. Both the influence of garlic (G) and of linseed oil (L) on survival was statistically significant. Combination of both interventions produced additive effects. In any case, life span of our control group (C) was similar or even longer than those reported in literature (13, 29, 30, 41). The analysis of the underlying mechanisms at present is only possible to a limited degree:

- Increased blood pressure needs early treatment to prevent damage to the vessel walls with its consequences for circulation of vital organs as well as unfavourable changes in cardiac mass and configuration. In previous investigations using higher dosages, we could confirm significant antihypertensive and cardioprotective effects of both diets (5, 8, 9, 14–19, 33). In the present study, arterial blood pressure, as measured during the period of compensation, was negatively correlated with life span if the total number of animals is taken into account. A formal regression shows that lowering of blood pressure by 1 mmHg corresponds to a prolongation of life span by about 2 days. However, the correlation within the various groups was not significant. Thus, a causal relationship between blood pressure and survival cannot be proved based on this correlation although an influence of the antihypertensive component complies with the expectation. In any case, the relative

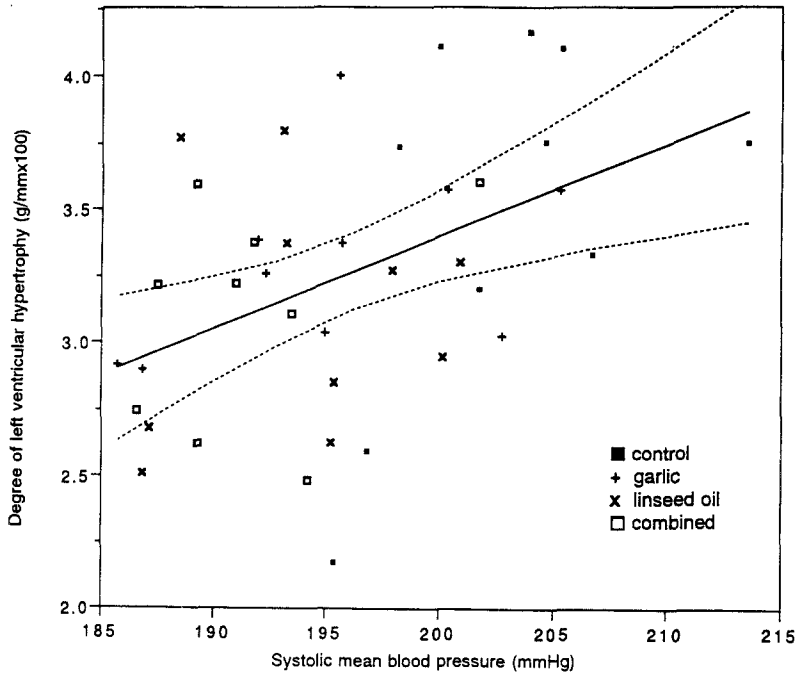

Fig. 6 Degree of left ventricular hypertrophy (ventricular weight related to tibia length) as a function of systolic arterial pressure. The slope of regression line is significantly different from 0 ($p < 0.001$). The broken curves show the 95 % confidence limits for the regression line.

slight decrease of blood pressure speaks in favor of a substantial influence of pressure-independent effects.

- Differences in the thickness of intima and media of arterial vessels between the four groups were not obvious at a qualitative histological evaluation. Furthermore, arteriosclerotic plaques were not evident in the large vessels and coronary arteries. Thus, antiatherosclerotic actions certainly were not decisive for the success of linseed oil and garlic treatment in this study.
- In close connection with the effects on blood pressure, the question arises as to what extent cardiac hypertrophy is affected by the long-term application of the diets and whether it influences survival. Despite increasing body weight with longer survival, mean left ventricular and right ventricular weight were lower in the treated groups. A statistically significant negative regression between relative heart weight and life span was conspicuous. Although this correlation cannot be shown within the individual groups, these results are consistent with the findings for blood pressure and the delayed development of cardiac insufficiency due to the dietary interventions.

The increase in heart rate after initial decrease can also be interpreted, at least in part, as an indication of pumping failure. Probably, the rapid early decline is not only an age-dependent phenomenon, but also due to accomodation of the animals to the procedure of measurement.

Garlic

Garlic has both the character of a spice and a drug. Favorable cardiovascular effects of garlic have been reported by many authors (for review see 11, 27, 32, 37, 39, 45, 47). Previous experiments by our group confirm favorable effects of garlic powder feeding on blood pressure (9, 18), plasma lipid profile, viscosity (9, 14), as well as antioxidative effects (33, 44). The latter effect may well be involved in the organ protective function of garlic, particularly in the presence of PUFAs, although reduced formation of O_2 radicals due to n-3 fatty acids was also reported in the literature (48). Modest ACE inhibiting action (45) could also be confirmed (33), which would be consistent with inhibition of fibrosis (9, 18), although the latter effect was not demonstrable in the present study. As mentioned above, atherosclerotic alterations were not obvious in either group of our investigation. However, recent observations on the Langendorff heart preparation of normal Wistar rats revealed that cardioprotection by garlic preparations is neither bound to the antihypertensive and atherosclerotic actions nor to the presence of thrombocytes. Significant reduction of ischemic zone size and reduced susceptibility to ventricular arrhythmias after experimental coronary artery coarctation could be demonstrated (14, 16, 19). The latter protective effects were attenuated by inhibition of cyclooxygenase. Thus, the question arises as to what extent the prostanoid system is involved in the garlic effects (31). Unfortunately,

the findings are controversial; on the one hand, an inhibition of cyclooxygenase (45, 46), of incorporation of arachidonic acid into the thrombocytes (40) and inhibition of thromboxane synthesis (22) has been reported. On the other hand, a slight increase in the prostacycline metabolite 6-oxo-PGF1 has been found in the coronary effluent after feeding allium ursinum (33). This would mean that thromboxane and prostacycline synthesis are influenced in a different way. Whereas an increase in the membrane concentrations of phospholipids and cholesterol in erythrocytes has been described (6), no alterations in membrane fatty acid composition and double bond index were found in our experiments (14, 16, 19). Thus, the significance of garlic effects on the prostaglandin system remains a challenge for further investigations.

In the same way, the question needs further studies which ingredients and decomposition products of garlic (alliin/allicin, methylcysteinsulfoxide, alkylcysteines, glutamylpeptides, flavonoides, (adenosin)-mono-di-and trisulfides, thioles, thiosulfinates) (32, 45) are in detail responsible for the individual effects discussed above.

Linseed oil

The cardiovascular effects of PUFAs exhibit some similarities to those of garlic. Based on previous investigations by our group, it must be emphasized that we have to make a strict distinction between the effects of various oil diets. Linseed oil, which has been used in the present study, besides linolenic acid (18:3, n-3) contains significant amounts of linoleic acid (18:2, n-6). This is important in view of cellular interactions between n-6 and n-3 fatty acids (4, 23, 48). Lowering of blood pressure by application of linseed oil is controversial in the literature (7, 25, 35, 38, 43). In the present study as well as in most, although not in all former investigations by our group, the antihypertensive effects of linseed oil were significant (8, 14), as were reduction of plasma cholesterol and triglycerides (14), blood viscosity and elasticity (8), and reduced formation of the proinflammatory leucotriene B4 in favour of B5 (3). In addition, anti-ischemic and antiarrhythmic actions could be demonstrated in the Langendorff heart preparation after experimental coronary occlusion although these effects were less pronounced as compared to those of fish oil (14, 15, 19). In the given context, it is of particular interest that a diet rich in n-3 fatty acids was able to retard the development of left ventricular eccentric configuration in hypertensive rats (5).

After addition of 10 % linseed oil to the standard chow, an incorporation of n-3 fatty acids (18:3, n-3; 20:5 n-3; 22:6 n-3) into the membrane phospholipids was found; there was also a moderate increase in 18:2, n-6 at the expence of 20:4, n-6 and 22:4, n-6 (2). However, the implications of an altered n-3/n-6 ratio in the membranes and a reduced formation of arachidonic acid (20:4, n-6) have not yet been completely clarified. One consequence of the incorporation of n-3 fatty acids in the membrane is the increase of the double bond index which has been found to be correlated to the antiarrhythmic effect (15); the changes in membrane fluidity are assumed to play an additional role.

Without doubt, the fatty acid composition of membrane phospholipids influences the formation of prostanoids, and the reduced synthesis of arachidonic acid derivatives by dietary n-3 PUFAs (2, 12, 23) is considered to be an important mode of action. This hypothesis would be supported by the finding in our material that a low sarcolemmal concentration of arachidonic acid was correlated with a low incidence of ischemia-induced fibrillation (19). On the other hand, the cardioprotective effects of all PUFAs under ischemia and reperfusion could be completely abolished by cyclooxygenase inhibition in contrast to a partial neutralization in the garlic group (14, 15, 19), indicating a protective action of prostacyclin (PGI2 or PGI3) (21, 26, 36). Although the observations of Ohkubo et al. (28) as well as those of Bordet et al. (4) suggest complex and unexpected pathways of prostacyclin (I2/I3) synthesis, it can be ruled out that the protective actions are exclusively related to influencing the antagonism between prostacyclin (I2 or I3) and thromboxane (TxA2 or TxA3) (15, 19, 42).

Thus, concerning the mode of action, there remains a number of problems to be solved. Nevertheless, there is no doubt that both dietary interventions applied in this study prolonged life span due to retarded manifestation of cardiac failure. Assuming that the results of the G+L group (prolongation of life span by 14 %) could also be applied to human beings, this would mean, e.g., that a hypertensive patient reach an age of 82 instead of 72 years. Of course, species-dependent pecularities in the response must be taken into account (1). In any case, the present study indicates that in clinical medicine it may also be worthwhile to consider the application of dietary cardioprotective interventions not only in case of coronary diseases but also in case of impaired cardiac function due to mechanical overload.

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