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EFFECT OF ACUTE AND CHRONIC STRESS ON THE HEMOSTATIC BALANCE AND THE ROLE OF RENIN-ANGIOTENSIN SYSTEM

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Abstract

Stress is involved in the development of diseases related to abnormal hemostasis. Thrombosis may develop whenever the dynamic balance between prothrombotic and antithrombotic processes become altered. Recently, renin angiotensin system is considered to be a stress hormone response system. The aim of the present work was to clarify the effect of acute and chronic stress on the prothrombotic and antithrombotic activity and to study the role of angiotensin II in these stress-induced changes. The results of this work showed that acute ether stress and chronic isolation stress lead to suppression of both intrinsic and extrinsic coagulability manifested by a decrease in the fibrinogen concentration and a decrease in the activity of factors VII and X, at the same time acute and chronic stress caused a decrease in the antithrombotic activity indicated by a reduction in the activity of antithrombin III. This means that hemostatic balance is probably maintained at a low level this make it difficult to hypothesize the existence of a hypercoagulable or a hypocoagulable state during stress. These changes can not be attributed to hemodilution since we found that stress causes hemoconcentration indicated by increased packed cell volume. The results of this work showed, also, that these stress-induced hemostatic changes was prevented by pretreatment with the angiotensin converting enzyme inhibitor (perindopril), this means that these stress-induced hemostatic changes is mediated, at least partially, through the renin angiotensin system.

Introduction

Many studies point out that

stress is involved in the development of diseases related to abnor-

mal hemostasis, such as myocardial infarction, cerebrovascular ischemia and disseminated intravascular coagulation (Siess et al., 1982). On the other hand the coagulation and fibrinolytic systems act to counterbalance hemostatic phenomena and thrombosis may develop whenever the dynamic balance between prothrombotic and antithrombotic processes become altered (Hamsten et al., 1987 and Juhan and Collen, 1992). However the effect of stress on these systems has not been fully investigated.

Renin angiotensin system is considered recently by many authors to be a stress hormone response system similar to the hypothalamus-pituitary-adrenal cortex system and the sympathetic-adrenal medulla system (Yang et al., 1996). Also, many authors reported that circulating and tissue angiotensin II may play an important role in the acute and chronic stress responses and that angiotensin II should be classified as a stress hormone (Yang et al., 1993). Also, it is reported by many authors that angiotensin II is in-

involved in many stress responses in the body as, stress analgesia (Haulic et al., 1986), hemodynamic response to stress (Gaudet et al., 1996 and Schmieder et al., 1996) and stress ulcer (Mou et al., 1998). However the previous reports on the effect of renin angiotensin system on the stress-induced changes in the clotting and anticlotting mechanisms are very little.

The aim of the present work was to clarify the effect of acute and chronic stress on the prothrombotic and antithrombotic activity and to study the role of angiotensin II in these stress-induced changes.

Material and Method

Experimental animal :- Adult male guinea pigs with a weight ranging between 350-450 grams were used.

Sample collection and assay procedure :-

Blood was taken directly from the heart under intraperitoneal anaesthesia with 50mg/kgm body weight sodium thiopental. Two samples were taken, the first one

on sodium citrate 3.2% (1 volume citrate to 9 volumes blood). This sample was immediately centrifuged in cooling centrifuge and plasma was separated and estimated for prothrombin time (P.T.) (Hirsh et al, 1992), partial thromboplastin time (P.T.T) (Muntean et al., 1992), thrombin time (T.T) (Robertson et al., 1975) fibrinogen concentration (Fn. Cone.) (cooper and Douglas, 1991), factor VII activity (F VII) (Furie and Furie, 1988), factor X activity (F X) (Furie and Furie 1988) and antithrombin III activity (A.T.III) (Karges and Heimburger, 1987). All kits were supplied by Dade Behring company⁵, Germany, except the kits for thrombin time determination was supplied by Diamed company, Switzerland.

The second sample was taken on ethylene-diamine-tetra-acetic acid (EDTA) for determination of packed cell volume (P.C.V.) to find out the presence of hemoconcentration or hemodilution which might affect the coagulation mechanism.

Groups of experiments :- This study included 5 groups each

group consisted of 8 guinea pigs:-

Group 1 (control group):- Consisted of normal animals not subjected to acute or chronic stress and not injected angiotensin converting enzyme inhibitor (ACE inhibitor).

Group 2 (acute stress group):- In which the effect of acute ether stress on the blood clotting and anticlotting mechanisms was studied. The animals of this group were exposed to ether stress for 3 hours by putting them in a container saturated with ether vapor for approximately 1 minute until unconsciousness was 'reached'. Then, they were removed and placed in another container and were maintained unconscious by continuous dribbling of ether.

Group 3 (chronic stress group):- In which the effect of chronic stress on clotting and anticlotting mechanisms was studied. The animals of this group were subjected to chronic isolation stress for 4 days by putting them separately in small dark cages.

Group 4 (Acute stress ACE inhibitor injected group):- In which

the effect of angiotensin converting enzyme (ACE) inhibitor, perindopril (coversyl) (Servier, Egypt industries limited) on acute stress-induced changes on blood coagulation and anticoagulation mechanisms was studied. These animals were injected perindopril (coversyl) 4 mg/kgm body weight/day intraperitoneally (I.P.) for five doses starting 4 days before exposure to ether stress.

Group 5 (chronic stress ACE inhibitor injected group):- In which the effect of ACE inhibitor on chronic stress-induced changes in prothrombotic and anti-thrombotic mechanisms was studied. These animals were injected perindopril 4mg/kgm/day I.P. for 5 doses starting the day before isolation.

Statistical analysis:- student t-test was used to compare the mean values. Differences with P value < 0.05 were considered statistically significant.

Results

* Effect of acute and chronic stress on the clotting and anticlotting mechanisms :-

Table (1) and figure (1) showed that both acute ether stress and chronic isolation stress caused a significant decrease in fibrinogen concentration ($p < 0.01$), factor VII activity ($p < 0.001$), factor X activity ($p < 0.001$) and antithrombin III activity ($p < 0.001$) while the decrease in prothrombin time, partial thromboplastin time and thrombin time was non significant. This table and figure showed, also, that stress caused a significant increase in packed cell volume

* Effect of angiotensin converting enzyme inhibitor (perindopril) on the stress-induced hemostatic changes :-

Tables (2) and (3) and figures (2) and (3) showed that pretreatment of animal with perindopril prevented the reduction in fibrinogen concentration and activity of factors VII and X and antithrombin III induced by stress and also, it prevents the increase in the packed cell volume induced by stress, while the effect of perindopril on prothrombin, partial thromboplastin and thrombin times was non significant.

Table 1 : The effect of acute and chronic stress on the clotting and anticlotting mechanisms and PCV (Mean values \pm SD).

	PT sec.	PTT sec.	TT sec.	Fn.Con. gm/L	FVII %normal	FX %normal	ATIII %normal	PCV %blood
Control (group 1)	35.9 \pm 2.3	23.6 \pm 2.9	16.3 \pm 2.9	1.78 \pm 0.3	75.6 \pm 4.3	102.5 \pm 7.6	72.5 \pm 3.1	38.9 \pm 1.1
Acute Stress (group 2)	38.9 \pm 3.3 N.S.	26.9 \pm 3.1 N.S.	17.5 \pm 1.5 N.S.	1.44 \pm 0.17* P<0.01	48 \pm 3.2* P<0.001	78.5 \pm 5.3* P<0.001	57 \pm 2.7* P<0.001	43.4 \pm 1.2* P<0.001
Chronic Stress (group 3)	38 \pm 3.1 N.S.	24.2 \pm 2.8 N.S.	17.06 \pm 1.4 N.S.	1.39 \pm 0.16* P<0.01	53.6 \pm 3.4* P<0.001	83.4 \pm 5.8* P<0.001	58 \pm 2.5* P<0.001	44.5 \pm 1.25** P<0.001

Table 2 : The effect of ACE inhibitor on the haemostatic changes induced by acute stress (Mean values \pm SD).

	PT sec.	PTT sec.	TT sec.	Fn.Con. gm/L	FVII %normal	FX %normal	ATIII %normal	PCV %blood
Acute Stress (group 2)	38.9 \pm 3.3 N.S.	26.9 \pm 3.1 N.S.	17.5 \pm 1.5 N.S.	1.44 \pm 0.17 P<0.01	48 \pm 3.2 P<0.001	78.5 \pm 5.3 P<0.001	57 \pm 2.7 P<0.001	43.4 \pm 1.2 P<0.001
Acute Stress + ACE inh. (group 4)	38.3 \pm 4.1 N.S.	23.8 \pm 2.9 N.S.	15.8 \pm 2.1 N.S.	1.8 \pm 0.19* P<0.01	73.1 \pm 4.1* P<0.001	95.8 \pm 5.9** P<0.001	73.6 \pm 3.9** P<0.001	37.3 \pm 1.1* P<0.001

Table 3 : The effect of ACE inhibitor on the haemostatic changes induced by chronic stress (Mean values \pm SD).

	PT sec.	PTT sec.	TT sec.	Fn.Con. gm/L	FVII %normal	FX %normal	ATIII %normal	PCV %blood
Chronic Stress (group 3)	38 \pm 3.1 N.S.	24.2 \pm 2.8 N.S.	17.06 \pm 1.4 N.S.	1.39 \pm 0.16 P<0.01	53.6 \pm 3.4 P<0.001	83.4 \pm 5.8 P<0.001	58 \pm 2.5 P<0.001	44.5 \pm 1.25 P<0.001
chronic stress + ACE inh. (group 5)	37.1 \pm 3.9 N.S.	23.8 \pm 2.7 N.S.	15.9 \pm 1.9 N.S.	1.65 \pm 0.15 P<0.01	76.1 \pm 4.2* P<0.001	98.2 \pm 4.1** P<0.001	70.5 \pm 3.1* P<0.001	39.1 \pm 1.1* P<0.001

• Significant decrease

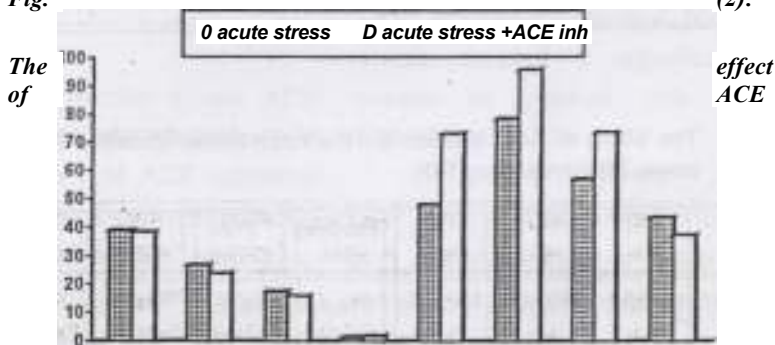
Significant increase

N. S. = Non significant.

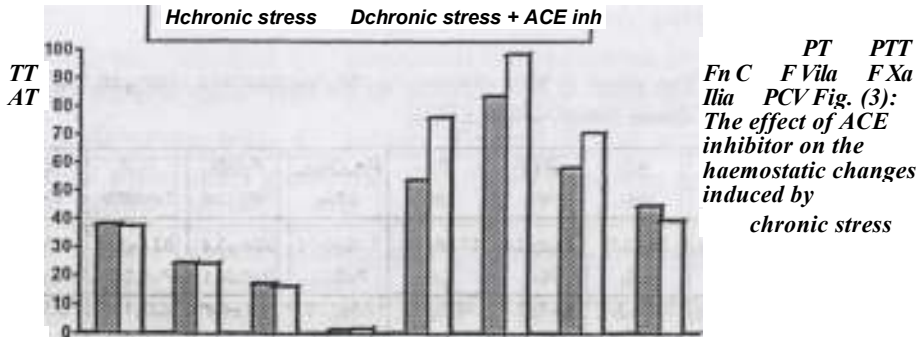
12	Dcontrol	Qacute stress		Echronic stress		
0-						
10						
0						
80						
60	fP&					
40						

PT PIT TT FnC F Vila FXa AT Ilia PCV Fig. (1):
The effect of acute and chronic stress on the clotting and anticlotting mechanisms and PCV

Fig. (2):



inhibitor on the haemostatic changes induced by acute stress



PT PTT
Fn C F Vila FXa
Ilia PCV Fig. (3):
The effect of ACE inhibitor on the haemostatic changes induced by chronic stress

Discussion

Our results showed that acute and chronic stress leads to suppression of both intrinsic and extrinsic coagulability manifested by a decrease in the fibrinogen concentration and a decrease in the activity of factors VII and X, at the same time acute and chronic stress caused a decrease in the antithrombotic activity indicated by a reduction in the activity of the antithrombin III. This means that the hemostatic balance is probably maintained at a low level, this make it difficult to hypothesize the existence of a hypercoagulable or a hypocoagulable state during stress. These changes can not be attributed to changes in blood concentration as we found that stress causes hemoconcentration indicated by increased packed cell volume which is expected to increase coagulability and not to decrease it.

The previous reports about the effect of stress on blood coagulation showed marked controversy. In agreement with our results, palmblad et al., (1977) found prolonged exposure of humans to chronic stress suppresses the ac-

tivities of intrinsic coagulation factors. Also, Hata et al., (1991) reported that, rats exposed to chronic cold stress exhibit suppressed intrinsic coagulability but normal extrinsic coagulability. In contrast to our results many investigators found that coagulation mechanisms are activated by different forms of stress as prolonged endurance exercise stress (Ponjee et al., 1993, Frisco et al., 1993 and Mustonen et al., 1998), noise stress (Chohan et al., 1984) and surgical stress (Bredbacka et al., 1986, Shinohara et al., 1997 and nguyen etaL, 1998).

Also the previous works on the effect of stress on the anticlotting and fibrinolytic mechanisms showed controversial results. Seyfer et al. (1981) confirmed our results by demonstrating a decrease in antithrombin III activity in elective surgery and trauma. Also, Tamura et al., (1996) found a decrease in fibrinolytic capacity in hyperthermal stress. In contrast to our results, Bartish et al., (1990) found that long distance running increased antithrombin III activity. Also, Hata et al., (1991) found an increase in the fibrinolytic activity

in rats exposed to chronic cold stress. Frisco et al., (1993) reported an increase in fibrinolytic activity after physical exercise stress. Also, Shinohara et al., (1997) found an increase in fibrinolytic activity during surgical stress.

This controversy in the hemostatic changes in the stress was explained by Hata et al., (1991) who reported that, hemostatic changes resulting from chronic stress present a complicated picture and appear to vary according to the type of stress. However, this explanation was not proved in our results as we used two forms of stress different both in duration and nature and their effect on clotting and anticlotting mechanisms was nearly the same. Another explanation for this controversy may be the difference in the experimental animal used, some investigators studied the effect of stress in humans, others used rats, other used Swine model and in our work guinea pig was used. A third and important explanation for this controversy in results is the difference in the parameters measured in each work and if they are sufficient for the final conclu-

sion or not. Most of the workers who found increased coagulability during stress either they go to this final conclusion by measuring only some anticlotting factors as in the work of Seyfer et al., (1981) and Tamura et al., (1996) or they measure only some clotting factors as in the work of Ponjee et al., (1993), Mustonen et al., (1998) and Nguyen et al., (1998). But those who estimated the clotting and anticlotting mechanisms, as we did in this work, found that! the hemostatic balance is maintained during stress and thus they can not confirm the existence of a hypercoagulable or a hypo coagulable state during stress and this I is similar to our final conclusion. And as hypercoagulable state develop whenever the dynamic balance between prothrombotic and antithrombotic processes become altered (Juhan and Collen 1992), thus those who tested only the clotting or the anticlotting mechanisms during stress have no sufficient data to conclude a presence of a hyper coagulable state during stress.

Our results showed, also, that injection of angiotensin converting

enzyme inhibitor (coversyl) prior to stress prevented the stress-induced decrease in the clotting factors (fibrinogen, factor VII and factor X). This means that the stress-induced change in the hemostatic process is mediated, at least partially, through the renin angiotensin system and thus we can conclude that the renin angiotensin system is a stress hormone response system and that angiotensin II is a stress hormone.

There are very little previous reports, if any, on the effect of renin angiotensin system and angiotensin converting enzyme inhibitors on the stress-induced change in hemostatic process, but many authors found that renin angiotensin system mediates a lot of stress responses, other than the hemostatic response, and that angiotensin converting enzyme inhibitors protect the body against these responses and they finally concluded that renin angiotensin system is a stress hormone response system. Mou et al., (1998) and Uluoglu et al., (1998) found that the endogenous angiotensin II plays a significant pathogenetic role in the development of stress ulcer.

Remme (1998) found that angiotensin II aggravate the short-term stress-induced myocardial ischemia and angiotensin converting enzyme inhibitors reduce it. Haulic et al., (1986) found the participation of the cerebral renin angiotensin system in the stress analgesia. Also, Gaudet at al., (1996) found that renin angiotensin system is involved in the rise of blood pressure induced by stress. Moreover, Yang et al., (1993) and Yang et al., (1996) found that circulating and tissue angiotensin II are significantly increased in both acutely and chronically stressed animals and humans and they finally reported that renin angiotensin system is a stress hormone response system and that angiotensin II should be classified as a stress hormone.

It can be noticed, also, from our results that angiotensin converting enzyme inhibitor (coversyl) prevented the reduction in the clotting and anticlotting mechanisms induced by stress and returned it nearly to the control value but does not increase it more than the control value. This might mean that, although renin angio-

tensin system mediates the stress-induced hemostatic response, it does not affect the normal hemostatic processes. In confirmation to this, the finding of Trifeletti et al., (1997) who found that angiotensin converting enzyme inhibitors given to hypertensive patients were without significant effect on the blood coagulation and the finding of Meyer et al., (1995) who found that angiotensin converting enzyme inhibitors given together with warfarin did not affect the pharmacodynamic effects of warfarin.

The mechanism by which angiotensin II mediates the stress response is not yet clear. Takatsu et al., (1995) and Jezova et al., (1998) reported that angiotensin II modulate the sympathoadrenal and hypothalamic pituitary adrenocortical activation during stress. Another mechanism was given by Haulic et al., (1986) who reported that, the participation of renin angiotensin system in the stress analgesia was indirect through release of opioid peptides. A third mechanism was given by Dzau (1998) who reported that angiotensin II participate in the stress

response through oxidative stress mechanism.

Finally, the results of this work are of academic and clinical interest. First, the finding that the hemostatic balance is maintained during stress make it necessary to reevaluate the cause of the thrombotic phenomena that usually accompany stress which might be due to vascular endothelium mechanism. Second, the finding that the renin angiotensin system mediates the stress response make the use of angiotensin converting enzyme inhibitors (commonly used as antihypertensives) is advised in hypertensive patients exposed to or liable to stress.

References

Bartish P., Haerberli A. and Straub P. W. (1990) : Blood coagulation after long distance running : Antithrombin III prevents fibrin formation. *Thromb Haemostas* (63) : 430-434.

Bredbacka S., Blomback M., Hagnevik K., Irestedt L. and Raabe N. (1986) : Pre- and post-operative change in coagulation and fibrinolytic variables during

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abdominal hysterectomy under epidural or general anaesthesia. *Acta-Anaesthesiol-Scand* 30 (3): 204-10.

Chohan I. S., Singh I. and Rai R. M. (1984) : Influence of noise on blood coagulation. *Thromb. Haemostas.* 51: 22-23.

Cooper J. and Douglas A. S. (1991) : Fibrinogen level as a predictor or mortality in survivors of myocardial infarction. *Fibrinolysis*, 5: 105-108.

Dzau V. J. (1998) : Mechanism of protective effects of ACE inhibition on coronary artery disease. *Eur-Heart-J.* 19 Suppl J: J2-6.

Furie B. and Furie B. C. (1988) : The molecular basis of blood coagulation. *Cell*, 53: 505-518.

Gaudet E., Blanc J. and Elghozi J. L. (1996) : Role of angiotensin II and catecholamines in blood pressure variability responses to stress in SHR. *Am J Physiol*, 270 (6 Pt 2): R 1265-72.

Hamsten A., Faire U., Walldi-

us G., Dahlen G., Szamosi A., Landou C., Blomback M. and Wiman B. (1987) : Plasminogen activator inhibitor in plasma: risk factor for recurrent myocardial infarction. *Lancet*, II, 3-9.

Hata T., Kawabata A. and Itoh-E. (1991) : Blood coagulation and fibrinolysis in SART-stressed (repeated cold-stressed) rats and drug effects on the altered hemostatic parameters. *Jpn-J-Pharmacol.* 56 (4): 403-12.

Haulic A. I., Neam Tu C., Stratone A., Petrescu G., Brani Steanu D., Rosca V. and Slatineanu S. (1986) : Evidence for the involvement of cerebral renin-angiotensin system (RAS) in stress analgesia. *Pain*, 27: 237-45.

Hirsh J., Dalen J. E., Deykin D. and Poller L. (1992) : Oral anticoagulants: Mechanism of action, clinical effectiveness and optimal therapeutic ranges. *Chest*; 102: 3125-3265.

Jezova D., Ochedalski T., Kiss A. and Aguilera G. (1998) : Brain angiotensin II modulates sympathoadrenal and hypothal-

lamic pituitary adrenocortical activation during stress. *J Neuroendocrinol*, 10:67-72.

Juhan V. I. and Collen D. (1992) : One the role of coagulation and fibrinolysis in atherosclerosis. *Annals of Epidemiology*, 2: 427-438.

Karges H. E. and Heimburger N. (1987) : Coagulometric determination of the activity of anti-thrombin III in plasma *Ann. Univ. SaravMed. Supp.*, 3: 105-107.

Knieriem L. K., Harris M. M. and George J. N. (1985) : Platelet activation and secretion associated with emotional stress. *Circulation* 71: 1129-1134.

Meyer B. H., Muller F. O., Badenhorst P. N., Luus H. G. and de-la-Rey N. (1995) : Multiple doses of trandolapril do not affect warfarin pharmacodynamics. *S-Afr-Med-J.* 85 (8): 768-70.

Mou D., Zhu X., Xu W. and Du R. (1998) : The pathogenetic role of endogenous angiotensin II in stress ulcer in obstructive jaundice rats. *Chin Med J (Engl)*,

111: 309-12.

Muntean W., Finding K. and Leschnik B. (1992) : Partial thromboplastin times are longer in healthy children than in adults. *Thromb. Haemorrh. Disorders*; 6: 23-25.

Mustonen P., Lepantalo M. and Lassila R. (1998) : Physical exertion induces thrombin formation and fibrin degradation in patients with peripheral atherosclerosis. *Arterioscler-Thromb-Vasc Biol.* 18 (2): 244-9.

Nguyen N. T., Luketich J. D., Shurin M. R., Schatz S., Tran Q., Ravid J. and Schauer P. R. (1998) : Coagulation modifications after laparoscopic and open cholecystectomy in a swine model. *Surg-Endosc.* 12 (7): 973-8.

Palmblad J., Blomback M., Egberg, N., Froberg J., Karlsson C. G. and Levi L. (1977) : Experimentally induced stress in man: Effects on blood coagulation and fibrinolysis. *J. Psychosom. Res.* 21: 87-92.

Ponjee G. A., Janssen G. M. and van-Wersch J. W. (1993) :

Prolonged endurance exercise and blood coagulation: a 9 month prospective study. *Blood-Coagulation-Fibrinolysis*. 4 (1): 21-5.

Frisco D., Panizza R., Guarnaccia V., Olivo G., Taddei T., Boddi M. and Gensini G. F. (1993) : Thrombin generation after physical exercise. *Thromb-Res*. 69 (1): 159-64.

Remme W. J. (1998) : Effect of ACE inhibition on neurohormones. *Eur-Heart-J*. 19 Suppl J: J 16-23.

Robertson G., Owen W. G. and Roberts G. R. (1975) : Detection of thrombin time. *G. Clin. Pathol.*, 22: 340.

Schmieder R. E., Schobel H. P., Gatzka C. E., Hauser W., Dominiak P., Mann J. F. and Luft F. C. (1996) : Effects of angiotensin converting enzyme inhibitor on renal haemodynamics during mental stress. *J Hypertens*, 14 (10): 1201-7.

Seyfer A. E., Seaber A. V., Dombrose F. A. and Urbaniak J. R. U. (1981) : Coagulation chang-

es in elective surgery and trauma. *Ann-Surg*. 193 (2): 210-3.

Shinohara M., Kurokawa H., Yoshihara-Y., Kikubu S., Kusano T., Horie K., Murakami N. and Nagai Nara-N. (1997) : Responses to surgical stress in blood coagulation and fibrinolysis, platelet counts and thromboxane B2 after esophageal cancer operation. *Rinsho-Byori*. 45 (2): 179-84.

Siess W., Lorenz R., Roth P. and Weber P. C. (1982) : Plasma catecholamines, platelet aggregation and associated thromboxane formation after physical exercise, smoking or norepinephrine infusion. *Circulation* 66: 44-48.

Takatsu H., Scheffel U. and Fujiwara H. (1995) : Sympathetic tone assessed by washout of iodine 125-labeled metaiodobenzylguanidine from the murine left ventricle-influence of immobilization stress and inhibition of the renin-angiotensin system. *J-Nucl-Cardiol*. 2 (6): 507-12.

Tamura K., Kubota K., Kurabayashi H. and Shirakura T. (1996) : Effects of hyperthermal

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stress on the fibrinolytic system.
Int-J-Hyperthermia. 12 (1): 31-6.

Trifiletti A., Barbara N., Scarmardi R., Bagnato L., Pizzoleo M. A., Nevoso A., Lasco A., Pedulla M. and Frisina N. (1997) :
Effects of medium-term antihypertensive therapy on haemostatic parameters in patients with essential hypertension. Haemostasis. 27 (1): 35-8.

Uluoglu C., Guney Z., Kilinc M., Bozkurt S. and Ercan Z. S. (1998) : The effects of captopril

and naloxone on restraint-cold-stress- and ethanol-induced gastric lesions in rats. Gen-Pharmacol. 30 (5): 701-4.

Yang G., Wan Y. and Zhu Y. (1996): Angiotensin II-an important stress hormone. Biol signals, 5: 1-8.

Yang G., Xi ZX, Wan Y., Wang H. and Bi G. (1993) :
Changes in circulating and tissue angiotensin II during acute and chronic stress. Biol Signals, 2: 166-72.