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# ENDOTRACHEAL ADMINISTRATION OF ADRENALINE IN CARDIOPULMONARY RESUSCITATION OF ANAESTHETIZED DOGS

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*In this study, we wanted to determine the effectiveness of endotracheal (ET) adrenaline administration on an anesthetized model of dog in hypoxia and cardiac arrest. We wanted to simulate the most frequent clinical state where urgent administration of drugs is necessary, but it's difficult to provide an intravenous (IV) route. Healthy dogs (n=37) were used for this study. They were anesthetized, endotracheally intubated and ventilated mechanically. A precordial lead II ECG was recorded throughout the experiment. The animals were provided with arterial and central venous lines. During the experiment we measured arterial blood pressure (SP, DP, MAP) by an invasive technique, central venous pressure by $H_2O$ manometer, hearth rate, acid-base value, glycemia and electrolytes. Control group: after IV adrenaline administration, concentrations in the arterial blood were continually measured. I exp. group: Under equal conditions, we used ET route for adrenaline administration whereby measuring their concentration and following their haemodynamic effects. In exp. group II adrenalin in a dose of 1.5 mg was administered endotracheally using the same tehnique as in group I. In the second part of the experiment, ET administration of adrenaline under conditions of cardiac arrest was studied. Hypoxia and cardiac arrest were induced by disconnecting from the breading machine. The influence of ET adrenalin administration on lung tissue were established by histophatological analysis and acid-base values. The maximum concentration of adrenalin in the blood after the ET route are almost equal to the concentrations of the drugs after IV administration, but ET doses of adrenaline must be higher than IV doses. Adrenalin was retained in the blood for a longer period after ET administration than after IV route. As the optimal solvent for adrenalin we recommend 0.9% NaCL, and we recommend using a long cateter via the endotracehal tube deep in to the tracheobronchial system as the optimal technique for ET administration. Hypoxia and cardiac arrest do not derange absorption of drugs after ET administration. By measuring the concentration of adrenalin in arterial blood following their haemodynamic effects in different experimental conditions and by evaluating the successfulness*

*of CPR and time necessary for the reappearance of heart action. We have concluded that there is no significant difference between the IV and ET administration of adrenaline.*

*Key words: adrenaline, endotracheal drugs, cardiac arrest*

## INTRODUCTION

Cardiac arrest is unquestionably the most dramatic situation which medical personnel may be faced with. In cardiac or respiratory arrest, the pathway of drug administration is as important as the selection of the drug itself. Pharmacological agents must reach the site of action as soon as possible. The pathway of administration has to be chosen in such a way to avoid metabolic or biochemical changes of the drug administered. During human or animal cardiorespiratory arrest, securing the intravenous pathway may be difficult or impossible. Venous collapse caused by former shock, hemorrhage, and injury of the extremities make access to peripheral veins difficult. In addition, some categories of patients are themselves a problem for provision of the venous pathway. This group includes newborns and infants, obese patients, drug addicts and hemodialysis patients. The option of an alternative pathway for urgent drug administration appears to be desirable in all the aforementioned cases.

Intrapulmonary (endotracheal-ET) way of drug administration in cardiopulmonary resuscitation (CPR) is considered an alternative method for intravenous drug injection (McIntyre *et al*., 1986; Vnuk *et al*., 1990). The idea to administer drugs via an endotracheal tube during resuscitation originates from Redding in 1967. He was the first to conduct the control study with ET drug administration during cardiac arrest. By inducing cardiac arrest by hypoxia on a dog model, he found that intravenous, intracardiac and endotracheal drug administrations were equally effective for circulatory collapse reversion. At the same time, some opposite attitudes have arisen based on the fact that an overall experience has been mostly gained from certain isolated cases, and therefore, scientifically documented experiments have been missing to verify the presence or absence of pulmonary pathological changes and to prescribe an optimal dose of a specific drug (Greenberg *et al.*, 1988; Orlowski *et al*., 1990).

Pharmacokinetics of drugs administered via the respiratory tract has not yet been fully known and has to be clarified (Crespo *et al*., 1991). The largest number of respective studies has been based on animal models. The lungs have a large drug absorption area (70 $m^2$). Moreover, the lungs accept the complete cardiac output, and accordingly a good distribution of the absorbed drugs is secured (Hasegawa *et al*., 1986; Hemberger *et al*., 1978). The benefit is noticed in an almost immediate drug absorption in the blood, evasion of first passage through the liver, and in case of pulmonary diseases, topical drug administration on the desired site of action.

In the study performed on anesthetized dogs, the objective was to establish the efficiency of endotracheal adrenaline administration: optimal endotracheal drug doses that would be equal to intravenous dosage; degree of resorption and

effectiveness of non-diluted and diluted forms of endotracheally administered adrenaline; pharmacokinetics of the drug administered via endotracheal tube (to achieve maximal blood concentration, and its maintenance, half-time of elimination, optimal timing for probable repeated doses) in comparison with intravenously injected adrenaline; effectiveness of endotracheal adrenaline administration in cardiac arrest; monitoring of hemodynamic parameters, acid-base balance and pathohistological changes of the lungs after endotracheal adrenaline administration in comparison with the effects following its intravenous administration.

## MATERIAL AND METHODS

The study included 38 mature healthy dogs of both sex mean body mass of 16.8 ± 3.4 kg. The experiment was carried out at the laboratory of the Institute of Pathophysiology, School of Medicine, Prishtina. Each dog was anesthetized by i.m. Ketamine injection (Ketalar) with 30 mg/kg. Upon being anesthetized, each dog was placed on the operating table and positioned on its right side, suitable for sternum compression and defibrillation. Standard ECG lead II was monitored by means of precordial electrodes (rate - 25 mm/sec). The whole experiment was video recorded.

After preparation of the femoral artery and vein, the catheter was inserted into the abdominal aorta. The other end of the catheter was connected by tap and transducer, to Siemens Sirecust monitor 400 for blood pressure measurements. The central venous catheter was inserted via the femoral vein into caudal vena cava. Venous line was used for administration of the required medicaments, being maintained by slow saline infusion. Central venous pressure (CVP) was measured by water manometer. All the time, the dog was breathing spontaneously with preserved pharyngeal and laryngeal reflexes. After this procedure, the anesthesia was deepened by i.v. injection of Fentanyl 0.03 mg/kg, while Pavulon 0.1 mg/kg was used for muscle relaxation. Dogs were endotracheally intubated and converted to mechanical ventilation (MV) of intermittent positive pressure ventilation type (IPPV) using Siemens-Servo respirator with the following parameters: respiration rate 16/min, tidal volume 10 ml/kg, I:E ratio 1:2, $FiO_2$ 0.5.

Cardiac action as well as heart rate and rhythm were recorded on a monitor, and ECG was performed using standard lead II. CVP was measured, and systolic, diastolic and mean arterial pressure (MAP) levels were recorded.

The experiment was set up into two parts.

In the first part of the experiment, the results of intravenous and endotracheal adrenaline administration in anesthetized dogs were analyzed.

*The controls (n=5)* were administered i.v. adrenalin (bolus injection, through CV catheter, in adose of 0.5 mg 1:1000, diluted with saline to 5 ml). Partially, after 30 seconds, 1 minute and 2, 3, 5, 10, 20, 30 and 60 minutes, arterial blood samples were obtained for measurements of serum adrenaline level. Blood samples were centrifuged, serum was separated and frozen until final determination of the given parameters. Arterial blood sampling was carried out for the determination of acid-base balance and gas analysis of arterial blood.

Hemodynamic parameters were monitored on regular basis throughout the experiment.

*In experimental group I (n=7)*, the experimental animals were administered adrenalin endotracheally, at a dose of 0.5 mg (diluted with saline to 10 ml), using a long aspiration catheter inserted deeply into the tracheobronchial trunk. Laboratory analyses of blood samples were performed and hemodynamic parameters were determined and monitored on regular basis as in the control group.

*In experimental group II (n=7)*, adrenalin in a dose of 1.5 mg was administered endotracheally, using the same technique as in Group I. All parameters were monitored as in the former experimental groups.

In the second part of the experiment, ET administration of adrenaline during cardiac arrest was studied. The experimental animals were assigned into three separate groups:

*Group I (n=7)*. Cardiac arrest was induced by MV break, and it was observed on a monitor. Different types of arrhythmia, time and duration, as well as types of cardiac arrest were recorded regularly. One minute after cardiac arrest, CPR, MV (reattaching to respirator with the same parameters) and external thoracic compression (80 compressions per minute) were initiated, as well as application of available medicaments such as i.v. Adrenaline in a dose of 0.5 mg, and, if required, 2% Xylocaine 1 mg/kg, Atropine 0.01 mg/kg and 8% Na-bicarbonate 1 mmol/kg. Defibrillation was performed (100 U), if required, by Siemens Theracard PM defibrillator. According to a specific scheme, blood samples were obtained for measurements of serum adrenaline level and acid-base balance in serum.

In all experimental phases the heart rate and rhythm, ECG, systolic, diastolic, mean arterial pressure (MAP) and central venous pressure (CVP) were regularly monitored and recorded.

*Group II (n=7)*. Cardiac arrest was induced in the same way in this experimental group as in group I, and CPR was performed by a standard procedure. Along with MV and external thoracic compression, ET administration of adrenaline in a dose of 1.5 mg, diluted in saline to 10 ml (3 times higher dose in relation to standard intravenous) was carried out using a long aspiration catheter inserted deeply into the tracheobronchial trunk. After adrenalin injection, the drug was dispersed to the periphery of the tracheobronchial trunk by means of 5 powerful AMBU balloon-assisted air insufflations. Subsequently, MV and closed cardiac massage were carried out. Other measures were performed in the same way as in group I.

*Group III (controls) (n=5)*. After hypoxia-induced cardiac arrest, resuscitation was applied as in the former two groups, but without adrenaline administration. Blood sampling was obtained in the same manner, with a close follow-up of the given parameters.

Adrenaline level in arterial blood serum was measured by spectrofluorometry using Spectrofluorometer Aminco-Bowman. Acid-base balance and gas analysis of arterial blood were determined directly by AVL apparatus.

The following pharmacokinetic parameters were calculated:

Cmax – maximal plasma adrenalin concentration

Tmax – time to achieve maximal plasma adrenalin concentration

Tther. – time to achieve therapeutical adrenalin concentration in plasma

Tmain. – time of maintenance of therapeutical adrenalin concentration in plasma

AUC 0-60 Area under curve – plasma drug concentration over time (t)

BAV - Bioavailability of drug represents a drug fraction which, after ET administration, reaches the systemic circulation and has the chance to exhibit its biological effect.

Upon the completion of the experiment, one dog from each experimental group was sacrificed, and thoracotomy was performed during which the pulmonary specimens were obtained from both lobes of the lungs. Lung tissue was fixed in 10% formalin, molded in paraffin blocks, microtomized and stained by a standard hematoxylin-eosin method.

Statistical analysis program Instat 2 was applied for statistical data processing. Depending upon the types of data, parametric (Student's t-test) and non-parametric (Mann-Whitney or U test and ANOVA) tests were used for statistical data analysis.

## RESULTS

In the first part of the experiment, in all three experimental groups no significant difference of basal values of (endogenous) adrenaline was found ($p>0.05$). In the control, serum adrenaline value increased to 110 ng/ml after 30 sec. of i.v. adrenaline injection, with a tendency to increase. Maximal serum adrenaline values in the controls were 320 ng/ml, being measured 1 minute after i.v. adrenaline administration. Thereupon, serum adrenaline values gradually decreased up to 20 ng/ml – data obtained from the femoral artery 60 sec. after i.v. injection (Figure 1).

In experimental group I, after ET adrenaline administration (0.5 mg), the values of serum adrenaline measured after 30 sec. were 86 ng/ml. In this group, maximal serum adrenaline values (measured in the second minute) were 132 ng/ml. Thereon, the measured values gradually decreased to 10 ng/ml at 60 minutes (Figure 1). Statistical analysis found a significant difference of serum adrenaline concentrations between the control and experimental group I ($p<0.001$). In experimental group II, following ET administration of adrenaline in a dose three times higher (1.5 mg) than the standard intravenous, after 30 sec., serum adrenaline concentration increased to 48 ng/ml, with a tendency to increase up to 300 ng/ml (i.e - maximal value measured at 2. minute). Thereafter, serum adrenaline values gradually decreased to 31 ng/ml at 60 min. (Figure 1). There was no significant difference of measured serum adrenaline values between the control and the experimental group II ($p>0.05$). At the same time a significant difference of serum adrenaline concentration was found between the groups I and II ($p<0.05$). Comparing the time of achieving the maximal adrenaline concentrations in all three groups, it could be noted that such time period was the

shortest in the control group – 60 sec. In group II, maximal adrenaline Changes of hemodynamic parameter values after i.v. adrenalin administration (control group)concentration was achieved after 2 minutes of measurement, and was maintained longer in circulation.

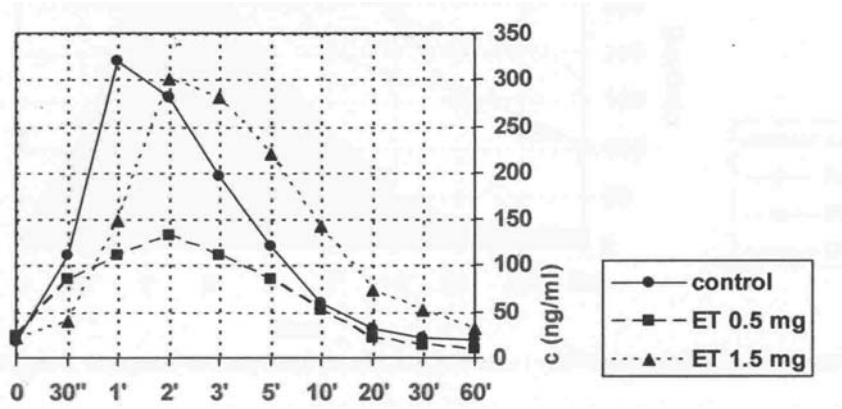



Figure 1. Changes of adrenaline blood concentration in the control group and experimental group I and II

Comparing the values of AUC (area under curve), it could be noted that AUC in the control group was 2082 ng/min/ml. In group II, after ET administration, due to a longer maintenance of adrenaline concentration in the circulation, AUC values were higher – 5.089 ng/min/mL.

BAV - bioavailability of adrenaline accounted for 61%, in distinction from the controls (i.v.), where BAV was 100%.

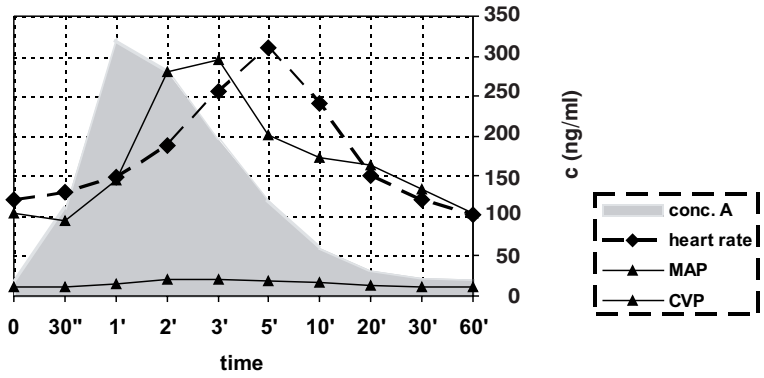



Figure 2. Changes of hemodynamic parameter values after i.v. adrenalin administration (control group)

At the same time, hemodynamic changes were monitored in all three experimental groups. Hemodynamic parameters followed the changes of serum adrenaline concentrations and became stable upon their elimination from the circulation.

In the control group, maximal values of 260 mmHg were achieved after 2 minutes. Maximal values of heart rate (250/min) were achieved 5 minutes after adrenalin administration (108% higher than basic value), when MAP values began to decrease. MAP and heart rate returned to initial values 30 minutes upon the beginning of the experiment. Measured CVP values followed the increase of MAP and reached the values of 20 cm $H_2O$ (90% higher than basic values), and they returned to initial values after 60 minutes (Figure 2).

It appeared that ET adrenaline administration in group I (0.5 mg) failed to yield effective hemodynamic response in experimental animals. MAP values increased only 9.5%, heart rate 16%, and CVP 20%. Hemodynamic parameter values returned to initial values 5 minutes upon adrenaline administration (Figure 3). Comparison of the changes of hemodynamic parameter values between the controls and group I showed a significant difference ($p<0.0001$).

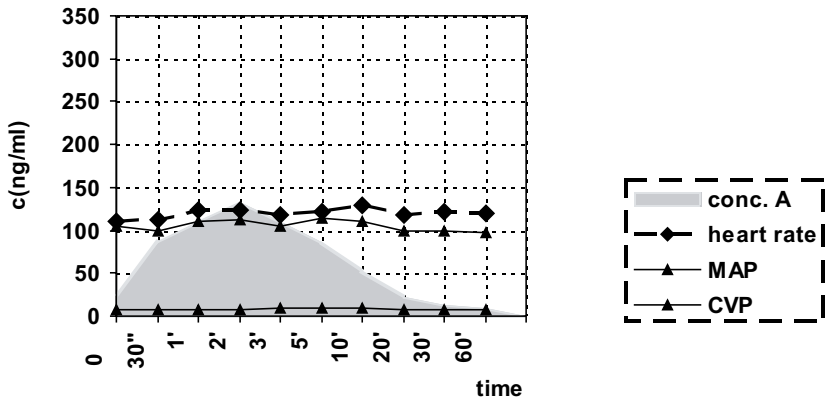



Figure 3. Changes of hemodynamic parameter values after ET adrenalin administration – 0.5 mg (group I)

Higher ET adrenaline dose (3 times) in group II produced a good hemodynamic response. MAP after 2 minutes increased by 143% of the basic value, heart rate – 123% of the basic value, and CVP – 135% in relation to the basic value (Figure 4). There was no significant difference of hemodynamic response between the controls (i.v.) and group II. However, a significant difference of hemodynamic response was found between groups I and II.

Both i.v. injection and ET administration of adrenaline caused different ventricular and supraventricular arrhythmias. According to the time of development and type of heart arrhythmia, we could not find the difference between i.v. and ET adrenaline administration. The most severe and most frequent arrhythmias developed 1 minute upon adrenaline administration (both in

the controls and ET groups): ventricular and supraventricular tachycardia, series of VES, multifocal VES, and bigeminy. Thirty minutes upon adrenaline administration, heart rhythm and rate returned to initial levels.

There were no significant differences of gas analysis results and acid-base balance between control values and after adrenaline administration in all three experimental groups ($p>0.05$).

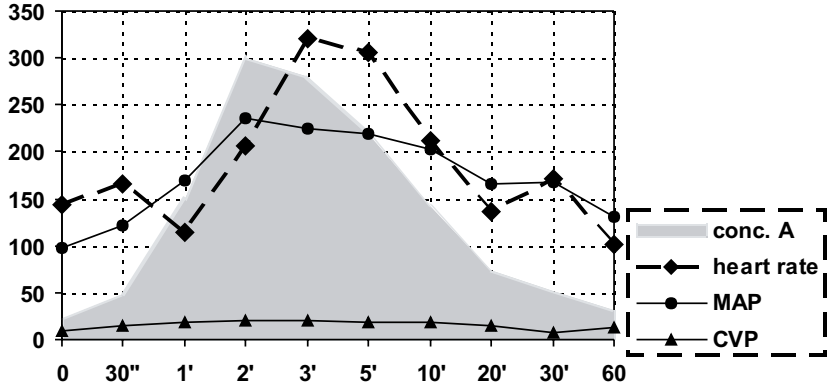



Figure 4. Changes of hemodynamic parameter values after ET adrenalin administration – 1.5 mg (Group II)

In the second part of the experiment, considering the fact that it proceeded under the same conditions until 1 minutes after cardiac arrest, certain conclusions can be reached regardless of the experimental group. Monitoring the heart rate in the period from disconnecting the breathing machine until the onset of arrest (apnea period), the initial increase of sinus tachycardia could be noted. Thereafter, different types of supraventricular and ventricular arrhythmias occurred, followed by ST segment depression with T wave inversion, ST elevation, bradyarrhythmia and finally cardiac arrest. Cardiac arrest by asystole developed in 12 dogs in asphyxia; by electromechanical dissociation occoured in 3 dogs, while ventricular fibrillation and VT without pulse could not be recorded in any of our cases. CPR was initiated one minute after cardiac arrest.

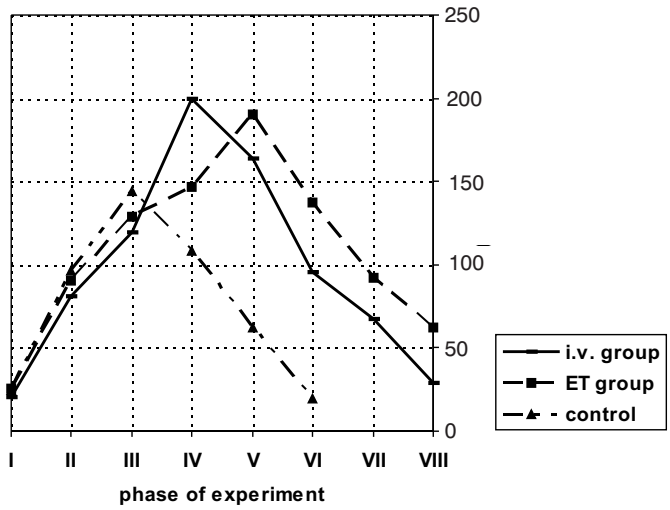
Estimation of the success of resuscitation in the control group of dogs (where adrenaline was not administered) revealed failure of CPR. One dog only, upon arrest by EMD type, developed fibrillation after 4 minutes of resuscitation. After the attempts of defibrillation, asystole occurred, which failed to respond to further CPR, so the resuscitation was ceased.

In group I (i.v. adrenaline injection), all 5 dogs were successfully resuscitated. Upon i.v. adrenaline injection, in a dose of 0.5 mg, sinus rhythm was restored in 4 dogs after a mean time of 60 sec. One dog, 60 sec. after adrenaline administration restored sinus rhythm with a frequency of 80/min, but 5 minutes later sporadic VES developed which became more frequent all the way to the onset of fibrillation. Upon i.v. 2% Xylocaine and defibrillation, sinus rhythm with a

frequency of 120/min was restored and it was maintained until the end of the 30 minute-resuscitation period.

In group II (ET adrenaline administration), 4 dogs were successfully resuscitated after a mean time of 80 seconds. One of them, 8 minutes after restored sinus rhythm, developed a series of VES and ventricular fibrillation. Defibrillation (100 U) resulted in sinus rhythm that was maintained until the end of the resuscitation period of 30 min. Cardiac action could not be restored in one dog upon cardiac arrest by asystole and after vigorous CPR, the resuscitation was ceased.

In the control group, basic values of adrenaline were 20.31 ng/ml. Only 3 minutes after cessation of breathing, serum adrenaline values considerably increased to 96.06 ng/ml. Until the onset of cardiac arrest, endogenous adrenaline values tended to increase, reaching their maximal values 1 minute after the arrest – 144.43 ng/ml. After this period, endogenous adrenaline concentration began to fall, which was measured 1, 3 and 10 minutes upon CPR, when serum adrenaline value dropped below basic values, i.e. to 19.41 μg/ml (Figure 5).




Phase: I anesthetized dogs
II 3 ' after MV break
III 1 ' after cardiac arrest
IV 1 ' after starting CPR (adrenaline administration)
V 3 ' after starting CPR
VI 10 ' after starting CPR
VII 20 ' after starting CPR
VIII 30 ' after starting CPR

Figure 5. Changes of adrenaline blood concentration during cardiac arrest and CPR in the control, and experimental group I and group II

In group I, endogenous adrenaline values were similar to the control group in the pre-arrest period. Namely, from basic adrenaline level of 20.3 ng/ml, serum adrenaline value increased to 81.4 ng/ml 3 minutes after breathing stopped, and 1 minutes after cardial arrest reached the value of 119.5 ng/ml. Following i.v. adrenaline injection in a dose of 0.5 mg, a considerable increase of serum adrenaline level was noted, reaching its maximum at 199.5 ng/ml 1 minute after adrenaline administration. Thereafter, these values decreased all the way to 28.6 ng/ml, 30 minutes after the beginning of resuscitation (Figure 5).

In group II, basic serum adrenaline values during asphyxia increased 3 minutes after cessation of breathing, from 25.2 ng/ml to 90.58 ng/ml, and to 129.2 ng/ml 1 minute after cardiac arrest. Following ET adrenaline administration in a dose of 1.5 mg, serum adrenaline values reached their maximum only 3 minutes after endotracheal administration (190.37 ng/ml). Then, serum adrenaline values started decreasing, and after 30 minutes of CPR, they were 62.0 ng/ml (Figure 5).

The following results were obtained by data processing:

Comparing the serum adrenaline values in pre-arrest period in all three experimental groups, Student's t-test failed to find any significant difference between these groups. Student's t-test found that during CPR there was a significant difference in serum adrenaline concentration between: the control and group I ($t=12.23$; $p<0.05$), and the control and group II ($t=3.11$; $p<0.05$).

Comparing serum adrenaline values during CPR between group I, (i.v. adrenaline injection), and group II (ET adrenaline administration), Student's t-test found no significant difference between these groups ($t=0.15$; $p>0.05$).

In all three groups, the experiment was carried out under equal conditions until CPR. The values of pH, $PaO_2$ and $PaCO_2$ were within normal limits in the initial arterial blood sample under basic conditions in anesthetized dogs. High $PaO_2$ of 405 mmHg should not be confusing, since mechanical ventilation with 100% $O_2$ concentration was applied to all dogs.

During the period of asphyxia, severe respiratory acidosis ($pH=7.08$; $PaCO_2=68.8$ mmHg) developed and $PaO_2$ dropped to 15.46 mmHg. One minute upon CPR, with 100%$O_2$ mechanical ventilation, arterial blood pH concentration started rising ($pH=7.28$), and became normal in measurements to follow. Thirty minutes after resuscitation, pH, $PaO_2$ and $PaCO_2$ returned to normal values. Statistical processing of results of arterial blood pH concentration found no significant difference between the studied groups ($p>0.05$).

## DISCUSSION

ET administration of drugs was first reported by Clode Bernarde in 1857, when he described lethal outcome of a dog after ET administration of curare. Modern CPR standards and the American Health Association recommend ET pathway as an alternative in emergency drug administration, specially if the venous line is not available (Ward *et al.*, 1983).

Subcutaneous and intramuscular drug administration in CPR did not appear beneficial due to insufficient peripheral perfusion (cardiac arrest, shock).

On the other hand, intracardiac drug administration may be associated with multiple severe complications, such as pneumothorax, injury of the pericardium, laceration of coronary arteries, cardiac tamponade, and intramyocardial drug administration. CPR measures must be discontinued and put off during a relatively long procedure of intracardial injection (Reeding *et al*., 1987).

ET drug administration in CPR was tested on laboratory animals (Young *at al.*, 1979). Several researchers have demonstrated that drugs reach the systemic circulation much faster by ET administration. The level of absorption and physiological and pharmacological effects of ET administered adrenaline and atropine proved to be favorable in relation to the i.v. pathway. ET administered adrenaline in experimental animals with induced hypotension appeared to be resorbed well. It has been shown that dogs, after induction of histamine-related hypotension and following ET adrenaline administration, restored normal blood pressure rapidly and efficiently (Roberts *et al*., 1979).

Our study has reported a good resorption of adrenaline from the lungs in the state of shock or hypoxia, which also supports ET application in these conditions.

The first key issue we faced during our study is the dosage of adrenaline in this alternative pathway. Several studies on animals have suggested that doses as ten times higher as those of i.v. administration result in the same hemodynamic effects (Roberts *et al*., 1979; Ruinton *et al*., 1987). Yet, other experiments on monkeys have indicated that ET doses have to be equal to i.v. dosage (Ralston *et al.*, 1984). Our results (blood drug concentration, AUC, BAV, hemodynamic effects) have justified three times higher endotracheal adrenaline doses in relation to standard intravenous dosage.

One radionuclear study, using Technetium 99m in a mechanically ventilated patient, has shown that less than 3% of the administered dose reaches the pulmonary circulation. It may be the result of pulmonary disease, inadequate ventilation or binding to ET tube (Schanker *et al*., 1977). However, on the basis of AUC and BAV values of ET introduced adrenaline in our study, it was found that the proportion of absorption was high (about 60%), and that a 2-3 times higher dose, depending upon the drug, could resolve the problem.

Several additional aspects of ET pharmacology are worthy of special consideration. Other than drug dosage, kind of dissolvent, pH, osmolarity, quantity, mode, localization and technique of ET drug administration should be considered.

Contemplating on the optimal dissolvent, Greenberg *et al*., 1980., and Orlowski *et al*., 1990., have demonstrated that physiological solution is less harmful to lungs than sterile water. On the other hand, Reeding's original study suggests that the absorption of sterile water from the lungs is more rapid than of isotonic saline, resulting in a faster and better restoration of spontaneous circulation. Mace *et al*., 1987., Hahnel *et al.*, 1990., and Prengel *et al.*, 1993. believe that the type of dissolvent is even more significant for the extent of drug absorption from the lungs than the technique of administration itself, and they give preference to saline over sterile water. Our option for the dissolvent was also saline. Histological findings of the lungs, as well as gas analysis proved that it was not harmful to the pulmonary parenchyme.

The volume of fluid for drug dissolution is also essential. Small volumes of fluid will have an effect on lowering the extent of drug absorption. Reeding et al., 1987. showed that ET administration of 1 mg of adrenaline in anesthetized dogs was not effective, but if it was dissolved in 10 ml of saline, the same dose of drug produced a clinical response. If the drug is given in an amount of fluid too large, pulmonary surfactant may be damaged, changed or washed out, and it may produce the clinical picture of pulmonary atelectasis. Administration of a large volume of saline this way may produce a clinical picture similar to that of drowning (Orlowski *et al*., 1987.).

Several techniques of drug administration by endotracheal tubing have been described. Drug administration into the proximal end of the endotracheal tube is the simplest method. However, drugs given in this way reach only the trachea and major bronchi. Consequently, it is possible that a portion of the drug is deposited in the endotracheal tube wall. Deep ET drug administration through a catheter allows drugs to diffuse more towards the periphery and closer to the large absorption area of bronchioli or even alveoli in both lungs. Radiological studies (Powers *et al*., 1984.), using contrast medium, have demonstrated a small difference between deep and superficial ET drug administration.

The disadvantages of ET drug administration are as follows:

– necessity to discontinue mechanical ventilation

– introduction of a foreign body into tracheobronchial trunk, which may cause the damage of pulmonary parenchyme and interfere with its function.

In our study, gas analysis of arterial blood was performed before and after ET drug administration. The studies of Orlowski *et al.*, 1984; Weil *et al*., 1986. have indicated significant changes of arterial blood gas analysis with subsequent development of ventilation-perfusion abnormalities following ET adrenaline administration. These changes are more pronounced if the drug is dissolved in sterile water than in saline. In our study, comparison of gas analyses before and after ET drug administration failed to find a significant difference between observed groups. $PaO_2$, $PaCO_2$ and $O_2$ saturation were being maintained within normal limits during the experiment. Hypoxia and cardiac arrest bring about the changes of arterial blood gas analysis, which is the result of pathological events in the lungs and other vital organs (shock state), and is not associated with ET drug administration.

Pathological examination of pulmonary tissue specimens did not reveal any changes that could have been caused by ET drug administration. The manifestation of intraalveolar and interstitial edema with micro thrombi as well as bleeding in alveoli and interstitium in specific experimental groups are explained by the state of hemorrhagic shock and hypoxia that were deliberately induced in these experimental groups, and not by the effect of ET drug administration. Mace et al., 1990. also studied the effect of ET drug administration on the condition of pulmonary parenchyme in different clinical conditions and could not find any significant changes.

Comparing the achieved adrenaline concentrations in arterial blood after i.v. adrenaline injection in a dose of 0.5 mg (controls) and ET adrenaline administration in the same dose, it may be noted that peak concentrations after

ET administration are low and apparently insufficient to produce a hemodynamic response (Figure 1). Clinical response after ET adrenaline administration in the same dose as in i.v. group is poor, changes of heart rate and MAP are minimal and not significant (Figure 3). AUC after ET adrenaline administration is 60%, which is apparently insufficient for a therapeutical effect . Lower AUC values by 40% in ET group in relation to i.v. group (AUC=100%) is accounted by adhesion of adrenaline droplets on syringe walls, catheters, endotracheal tubes and parts of tracheobronchial trunk where drug absorption is not possible. Maximal adrenaline concentrations in arterial blood after ET administration are approximately equal to half of peak concentration in i.v. administration (Figure 1). For this reason, we decided to increase the adrenaline dose, and accordingly, the group II was administered a 3 times higher dose (1.5 mg) of ET adrenalin.

Maximal adrenaline concentrations in arterial blood after ET administration of a 3 times higher dose than in i.v. application were achievedwith a delay in relation to i.v. group (measured at 2 minutes) and are almost equal to maximal adrenaline concentrations in the control group. However, maintenance of adrenaline concentration in the circulation is considerably longer in ET group than in i.v. group (Figure 1). There is no explanation for this depot phenomenon. One of the probable reasons is a prolonged absorption of adrenaline from the lungs as adrenaline deposited in the tubing and tracheobronchial trunk, and then, under the influence of positive pressure, during mechanical ventilation, it subsequently reached the alveolocapillary membrane and systemic circulation.

Half time of elimination of adrenaline is very short and its ET administration effectively bypasses venous circulation and provides direct access to arterial circulation where it has its maximal effects (Roberts *et al*., 1979). Hemodynamic changes after ET adrenaline administration (at three times higher doses than i.v.) appear to be equal to those after an i.v. adrenaline injection. Hemodynamic response is reflected in the maximal manifestation of alpha effects – vasoconstriction of peripheral blood vessels, leading to an extreme increase of MAP (x=260 mmHg). The highest arterial blood pressure levels measured in one dog were 360/240 mmHg. MAP changes are followed by CVP which rises to x=20 cm $H_2O$. Beta effects become manifest even 30 minutes upon ET adrenaline administration, but it achieves its maximal value only when MAP value begins to decrease (<200 mmHg). The reason for this “delayed” achievement of maximal heart frequency is high peripheral vascular resistance and “after load”, thus preventing the heart pump to attain maximal frequency under the influence of beta stimulation of exogenous adrenaline. Hemodynamic parameters are associated with changes of serum adrenaline concentrations, and therefore, after ET adrenaline administration, hemodynamic response is longer in relation to the i.v. group.

Cardiac arrest is unquestionably the most frequent and most dramatic situation where ET adrenaline administration is indicated, specially in cases when i.v. line is not provided. That is why we have tried to determine the efficiency of ET adrenaline in anesthetized dogs with cardiac arrest (Safar 1984).

Time of the apnea period (from the instant the respirator is discontinued until the onset of cardiac arrest) is considerably longer on the observed dog models in

our study when compared with the time reported in other studies on porcine model or clinical trials on humans (Lindner *et al*., 1989).

In our study, cardiac arrest was induced by asphyxia. Anoxia has a powerful direct effect both on the supplying blood vessels and to the heart muscle. That was the reason for developing of different arrhythmias during asphyxia in our study.

Hypoxemia and hypercapnia bring about the initial increase of heart frequency. Acute respiratory acidosis causes blood vessel smooth muscles to relax and stimulates the sympathetic nervous system. It results in vasodilatation, tachycardia and increased cardiac output (Gannong *et al*., 1991). The initial tachycardia is also caused by stimulation of chemoreceptors in carotid and aortic bodies due to hypoxia and fall of arterial pressure.

Cardiac arrest was detected by monitoring of II standard ECG lead. Occasionally, heart sounds were auscultated by precordial stethoscope. The experiments on dogs have shown that their heart sounds are not audible when systolic pressure reaches the level of 50 mmHg (Young *et al*., 1979).

In our study, 80% of cases developed cardiac arrest by asystole type, while ventricular fibrillation did not develop at all. This was not expected since ventricular fibrillation was, in 62%-85% of described cases, was reported to be most frequent after massive myocardiac infarction, as well as in all those conditions which cause oxygen deficiency, i.e. suffocation, drowning, heavy bleeding, etc.

It appears that absorption in endotracheal adrenaline administration is achieved at almost the same speed as in i.v. application, but the increase of serum concentration (Kuhn *et al*., 1981.) is lower and delayed, as to some extent, is confirmed by our study. Namely, peak serum adrenaline concentration is reached 1 minute after i.v. injection and 3 minutes after ET administration. These maximal values of serum adrenaline being nearly the same (there is no significant difference).

Persistence of some authors to prove the prolonged resuscitation period after ET adrenaline administration could not be justified by the time difference of 20 sec. obtained in our study.

On the basis of the results obtained by comparison of effectiveness of i.v. and ET adrenaline administration, our conclusion is that these two ways of adrenaline administration in CPR produce the same results.

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## ENDOTRAHEALNO DAVANJE ADRENALINA U KARDIOPULMONALNOJ REANIMACIJI ANESTEZIRANIH PASA

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### SADRŽAJ

U ovoj studiji su prikazani rezultati ispitivanja efikasnosti endotrahealne (ET) aplikacije adrenalina na modelu anesteziranog psa u uslovima hipoksije i srčanog zastoja. Na ovaj način su simulirana najčešća klinička stanja gde je urgentno davanje lekova neophodno, a istovremeno je teško ili nemoguće obezbediti intravenski (i.v.) put. U prvom delu eksperimenta praćene su promene koncentracije adrenalina u arterijskoj krvi anesteziranih pasa nakon ET aplikacije u različitim dozama (zavisno od eksperimentalne grupe) i upoređivane sa rezultatima dobijenim posle intravenskog davanja. Na osnovu registrovanih koncentracija leka u arterijskoj krvi i kliničkih manifestacija, može se zaključiti da ET davanje adrenalina u 3 puta većoj dozi od standardne ne zaostaje za i.v. davanjem. Osim toga, patohistološkie promene isečaka pluća i gasne analize arterijske krvi nisu ukazale na oštećenje plućnog parenhima nakon ET davanja adrenalina.

U drugom delu eksperimeta je ispitivana efikasnost ET davanja adrenalina u stanju akutnog zastoja srca. Hipoksija i zastoj srca ne remete apsorpciju adrenalina posle ET davanja. Na osnovu merenja koncentracije adrenalina u arterijskoj krvi pasa, kontinuiranog praćenja hemodinamskih efekata, procene uspešnosti kardiopulmonalne reanimacije i vremena potrebnog za uspostavljanje srčane akcije može se zaključiti da ne postoji značajna razlika izmedju i.v. i ET davanja adrenalina u akutnom zastoju srca anesteziranih pasa. ET dat adrenalin postiže maksimalnu koncentraciju u krvi nešto kasnije u odnosu na i.v davanje, ali se i duže zadržava u cirkulaciji.