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Effect of Adriamycin on Blood Flow in Renal Tumour and Normal Renal Tissue

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Abstract—*The effect of adriamycin (Adm) on local blood flow was simultaneously measured in neoplastic tumour, diameter* 3–5 mm, *and intact tissue in rat kidneys using the* H_2 *gas washout technique. Constant rate i.v. infusion of Adm,* 0.3–6 mg/kg/min *for* 3–15 min, *increased mean arterial blood pressure (AP) by* 20%, *a maximum already obtained at the lower infusion rate, without affecting heart rate. Control tumour flow averaged* 0.9 (0.4–1.1) ml/min/g. *Flow was inversely related to Adm infusion rate in both tissues, but tumour flow tended to be relatively less affected. In another series of experiments total renal blood flow (RBF) was recorded electromagnetically during constant rate infusion of Adm into the renal blood stream,* 0.03–3 mg/kg/min *for* 3–20 min. *AP increased and RBF decreased during the first* 2 min *of infusion, whereafter steady levels were maintained. Both parameters returned to control levels within* 4 min *after completed infusion, irrespective of infusion rate and duration. High i.a. infusion rates,* 2–3 mg/kg/min, *almost stopped RBF but gave no further AP increase (max at* ~0.5 mg/kg/min), *indicating a direct constrictor effect on renal vessels. On the other hand, the AP response persisted when renal circulation was excluded, suggesting a general pressor response evoked by Adm. A* 60% *RBF reduction was obtained by* 1 mg/kg/min *i.a. as compared to* 4–6 mg/kg/min *i.v. infusions. This indicates that a several times higher Adm concentration was maintained in renal blood during i.a. infusion. Taken together with the recovery time, this observation also suggests a post-infusion blood clearance of Adm with an initial half-time of about* 2 min *or less. This was confirmed in additional experiments where* [^{3}H]*-labelled Adm was determined in timed blood samples.*

INTRODUCTION

ADRIAMYCIN (doxorubicin), an anthracyclic agent with antitumour activity, is used in the therapy of a variety of malignant diseases. The pharmacokinetics, the pharmacology and the chemotherapeutic activity of this agent in laboratory animals and in man is extensively investigated and reported in the literature [1–10]. Its multipotential molecular character allows binding with numerous biologic components, the toxic effect on the myocardium being a serious adverse and dose-limiting effect.

Two different types of cardiotoxicity are described. First, acute and transient arrythmias and decrease of left ventricular ejection fraction [11], and second, the clinically more important cardiomyopathy, depending upon the cumulative dose and usually appearing within 2 months in humans [12].

There might, however, be hemodynamic effects of adriamycin (Adm) arising from other mechanisms than the cardiotoxic effects. Herman *et al.* [13] demonstrated transient hypotension in anaesthetised beagle dogs after rapid i.v. administration of up to 3 mg/kg of Adm. This effect was almost completely eliminated by blocking the histamine activity, indicating that Adm can act as a releaser of vasoactive substances.

Very little is known of the effect of Adm on peripheral vascular beds, a problem that should be worthwhile studying as selective i.a. administration of Adm has been taken into use [14–20]. Working with an experimental model of renal neoplasm, we observed that Adm infused as an i.a. bolus affected renal blood flow and arterial blood pressure. We therefore decided to take a closer look at the vasoconstriction elicited by Adm using constant rate i.v. infusion in rats. For repeated parallel measurements of local blood flow in tumour

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and intact renal tissue we chose the H_2 washout method [21], as previously used by us in the same experimental model [22]. This method provides measurements at about 5-min intervals. To describe the time course of total renal flow changes induced by Adm we recorded RBF electromagnetically during constant-rate infusion of Adm directly into the blood stream of the autoperfused kidney.

MATERIALS AND METHODS

Adriamycin (Farmitalia, Milan), containing 5 mg lactose per mg doxorubicin, was dissolved in 0.9% saline a few minutes prior to administration.

All rats were kept fasting with free access to water for one day prior to the experiments. They were anaesthetised with pentobarbital-Na, 50 mg/kg, and tracheotomised. The body temperature was maintained at 37–38°C by thermostatic control of a heating pad via a rectal thermistor. Systemic arterial blood pressure (AP) and heart rate (HR) were monitored from an arterial catheter with a Hewlett Packard transducer and recorder. Following surgery as described below, a recovery period of about 30 min was allowed.

Local flow measured by H_2 gas washout technique

The animals were laparotomised and the left kidney was gently immobilised. Two to four platinum electrodes, 0.1 mm diameter, were placed with the sensitive tip 1–3 mm deep into the renal tissue. Hydrogen concentration around the electrode tips was determined polarographically at a polarisation potential of +0.17 V versus an Ag/AgCl electrode placed subcutaneously. The amplified electrode current was recorded on a 6-channel recorder (Rikadenki Kogyo Co Model B-64). During steady AP, the animals were given inhalation air containing 5% H_2 to the tracheal cannula until constant H_2 concentration was obtained at the electrode sites. The H_2 was suddenly withdrawn and the washout curves were recorded. Local renal blood flow (LRBF) was calculated from the slope of the plotted semilogarithmic curves. For details on the method see Aukland [21] and an earlier report from this laboratory [22]. Control flow at each electrode site was calculated as the mean of two or more consecutive washout rates.

Pilot experiments. These were made in eight Wistar rats, body weight 350–430 g: a bolus of Adm, 1 mg in 1 ml 0.9% saline, was injected in half a minute into the upper part of the descending aorta through a carotid catheter. As renal H_2 saturation was established prior to the injection, the H_2 washout recordings began about 10 sec after completed injection. In order to evaluate the effect of the injected volume, washout recordings were made after a bolus injection of 5 mg lactose in 1 ml saline in five of the animals prior to the Adm injection.

Control experiments. These were made in another eight Wistar rats: H_2 washout rates were recorded during constant intravenous infusion of Adm, 2–6 mg/kg/min, through a femoral catheter. One or two washout registrations were obtained at a steady AP during infusion. The infused volume varied from 0.3 to 0.8 ml/min, the infusion time from 4 to 12 min. In three of the animals another washout was recorded 5 min after completed Adm infusion.

Local blood flow in kidneys with neoplasm. Local blood flow was determined in a third series of experiments: seven inbred Lister rats of both sexes with body weight 180–210 g were studied. One week prior to the flow measurements the animals were anaesthetised with ether and laparotomised. Transplantable tumour tissue was obtained from donor rats with 20-methylcholantrene-induced sarcoma (obtained from Sahlgrenska Sjukhuset, Gothenburg). The sarcoma was developed in this strain in 1968 and is now in its 175th transfer generation (1980). The tumour was exposed in the donor rat and approximately 1 mm^3 of tumour tissue was sampled and immediately deposited by a trochar technique into the lower pole of the left kidney in the recipient rat [23]. The abdominal wall was closed and the animals recovered.

The rats were prepared for H_2 washout recordings as described above. One or two electrodes were placed with the sensitive tips 1–3 mm deep into the intact renal tissue and one or two other electrodes were placed into the tumour. The tumour diameter averaged 4 mm (range 3–5 mm). Blood flow in tumour and intact tissue was determined from two or more H_2 washout curves during control conditions and one or more washout curves during i.v. infusion of Adm. Four animals received 0.3–1 and three received 4–5 mg/kg/min by intravenous infusion lasting for 3–15 min.

Electromagnetic flow measurement

Flow measurements made in three of the control experiments 5 min after completed i.v. infusion of Adm suggested a rapid flow recovery which could not be accurately described using the H_2 gas washout method. Thus, in order to detect rapid changes in total renal blood flow and to compare the effects of i.a.

and i.v. infusions of Adm we made a fourth series of experiments.

Seventeen Sprague–Dawley rats, body weight 220–280 g, were used. An extracorporal flow circuit was made according to Fink and Brody [24] to shunt blood from a carotid artery into an aortic pouch having the left renal artery as the only outlet. A flow probe (A/S Nycotron, Model 1607) with a 1.5 mm lumen diameter was interposed in the 20 cm long shunt. After surgery the abdominal wound was closed. Total renal blood flow (RBF) was measured with an electromagnetic flowmeter (A/S Nycotron, Model 376) and recorded together with AP [25]. Steady RBF and AP, as obtained 0.5 – 1 hr after surgery, served as control. Then 0.03 – 3.0 mg/kg/min of Adm was infused from a side branch into the shunt at a constant rate of 0.025–0.5 ml/min. Infusion time varied from 3 to 20 min.

In four of the rats Adm was dissolved in 0.5 ml saline and mixed with 0.5 ml blood 5 min before infusion. About 15 min later the infusion was repeated without blood in the infusate.

In seven of the rats a second, intravenous infusion was made 15 min after exclusion of the renal circulation by tightening snares prepositioned around the renal pedicles.

Blood clearance of adriamycin

The results of the electromagnetic flow measurements suggested that the concentration of Adm in arterial blood dictated the hemodynamic changes observed (cf. Discussion). Therefore, the time course of arterial blood Adm concentration following completed 10 min i.a. infusion of 0.5 mg/kg/min was determined in a fifth series of experiments using [^{3}H]-labelled Adm, 0.3 μCi/mg. In ten rats serial blood samples drawn at 2 min intervals from a carotid arterial catheter were counted (Packard Tri-Carb 460 CD liquid scintillation system) using a standard preparative procedure and correction for quenching.

RESULTS

The washout curves recorded in normal renal tissue and tumours before Adm was given were monoexponential down to a tissue H_2 saturation level of less than 25% in all experiments. The curves obtained during Adm influence were also monoexponential except in some of the pilot experiments, where four curves had a transient change of slope during washout and three had a permanent change.

Local blood flow in normal kidneys

For the pilot and control experiments the total range of local renal blood flow (LRBF) at the different electrode positions was 0.68–5.21 ml/min/g, average 2.24 ml/min/g, whereas AP averaged 110 mm Hg during control conditions. It should be emphasised that this LRBF value represents an unweighed average of high flow cortex, which accounts for about 70% of renal weight, and low flow medulla [22].

Pilot experiments. Bolus injection of 1 mg Adm (2–3 mg/kg) reduced LRBF at all electrode positions by an average of 43%, whereas a bolus injection of saline produced an insignificant increase (Fig. 1). The arterial pressure increased transiently during bolus injection, the maximum being indicated in Fig. 1. Control level AP was regained within 5 min following Adm injection. As compared to 0.9% saline, Adm had no statistically significant effect on HR or AP (Fig. 1).

Control experiments. Intravenous infusion of Adm decreased LRBF, as illustrated in Fig. 2 by the square symbols. A fairly similar increase of AP, average 20%, was obtained at infusion rates above 0.5 mg/kg/min. LRBF and AP were restored to control levels as determined about 5 min after the stop of Adm infusion in the three animals investigated. During Adm, heart rate was 95 ± 7% (S.D.) of control, i.e. not significantly altered.

No statistical correlation was obtained between the control flow level and the flow change observed at the different electrode sites in the pilot and control experiments.

Local blood flow in kidneys with neoplasm

Control LRBF averaged 2.73 ml/min/g (range 0.88–4.40), whereas tumour flow averaged

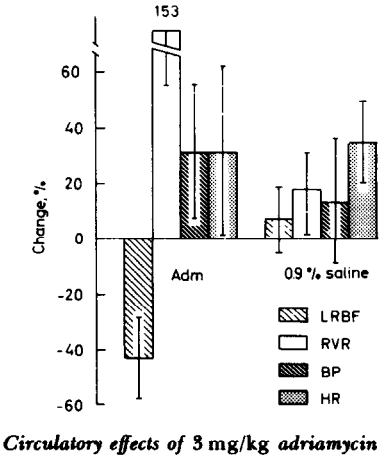

Fig. 1. Circulatory effects of 3 mg/kg adriamycin injected as a 1-ml bolus into the upper descending aorta in 30 sec. LRBF: local renal blood flow as determined by H_2 gas washout rate; AP: mean arterial pressure; HR: heart rate; LRVR: local renal vascular resistance. Bars indicate S.D.

0.87 ml/min/g (range 0.44–1.14), i.e. only 30% of the simultaneously recorded intact tissue flow. The coefficient of variation for consecutive flow measurements at the different electrode sites was 4.7% in intact tissue and 7.6% in the tumours. No statistical correlation was seen between control AP, 126 mm Hg (range 100–160) and control flow in the tumours.

The change of AP and intact tissue flow induced by i.v. Adm infusion corresponds well with those observed in normal kidneys, as illustrated in Fig. 2. The results in Fig. 2 indicate a relatively smaller average reduction of local flow in the tumour than in intact renal tissue, the difference being statistically significant ($P < 0.05$, two-tailed Student's t-test and Wilcoxon Rank Sum Test). In fact, flow increased in three of the four tumours studied during low Adm infusion rates (Fig. 2).

Time course of the pressor responses to adriamycin. The electromagnetic flow measurements made in normal kidneys gave an average RBF of 5.0 ml/min (range 3.6–6.3) at an average AP of 120 mm Hg (range 94–135). During i.a. infusion of Adm the RBF was reduced in 14 of the 17 animals ($P < 0.005$) depending on the infusion rate, as demonstrated in Fig. 3. Again, a 20% elevation of AP without altered HR was seen (cf. Fig. 2).

Figure 4 demonstrates that RBF and AP steady states were established after about 2 min of i.a. Adm infusion. Both these parameters returned to control levels within 4 min after stopping the infusion. The highest infusion rate, 3 mg/kg/min, almost stopped RBF but

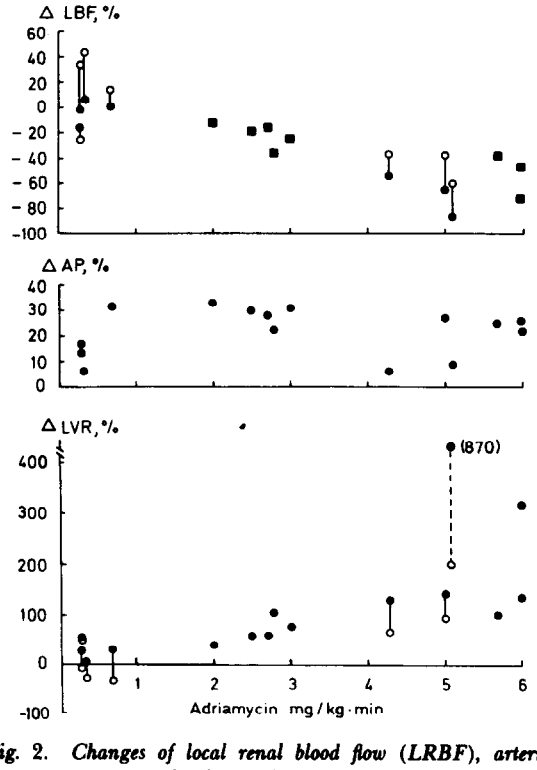

Fig. 2. Changes of local renal blood flow (LRBF), arterial pressure (AP) and local vascular resistance (LRVR) induced and maintained by constant rate intravenous infusion of adriamycin. Normal kidneys in control experiments: squares. Simultaneous measurements of LRBF in intact renal tissue and of local tumour flow are denoted by closed and open circles, respectively.

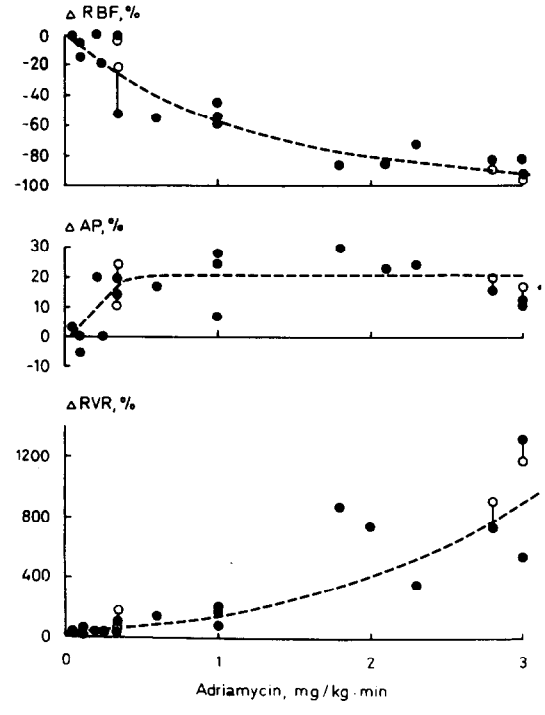

Fig. 3. Effects on electromagnetically recorded total renal blood flow (RBF) and arterial blood pressure (AP) induced and maintained by constant rate infusion of adriamycin into the renal arterial blood stream. Open circles indicate results obtained with blood added to the infusate. RVR: renal vascular resistance.

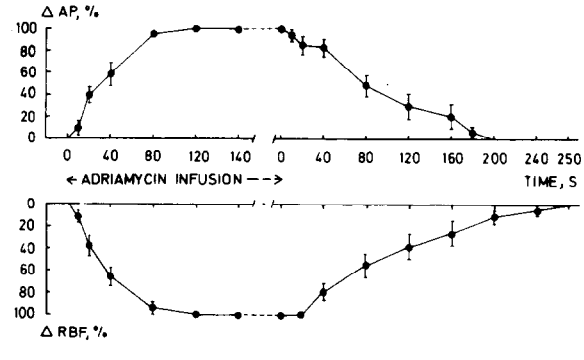

Fig. 4. The time course of the changes in mean arterial blood pressure (AP) and total renal blood flow (RBF) during constant rate i.a. infusion of adriamycin in the same experiments as in Fig. 3. Steady state levels, as obtained after 2 min, were maintained for the duration of the infusion which varied from 3 to 20 min. Normalised data: changes occurring in the initial and the recovery phases are calculated in % of the control to steady state differences, i.e. in % of the maximal change obtained in each experiment. Bars indicate S.E.

produced no additional AP increase. The AP increase induced by i.v. infusion of Adm after ligation of both renal pedicles was not different from that previously obtained by i.a. infusions in the same rats ($P > 0.3$). Ligation of the pedicles did not alter steady state AP *per se*. Similarly, mixing of blood and Adm solution prior to infusion apparently did not alter flow or pressure responses to Adm (Fig. 3).

Blood clearance of adriamycin

Within about 6 min following the completed 10 min i.a. infusion of Adm, 0.5 mg/kg/min, the systemic arterial concentration had dropped to about 20% of the peak reached during infusion (Fig. 5). The first two half-times averaged about 2 min each, the third being considerably prolonged. Flow and pressure responses in these experiments were closely similar to those indicated in Fig. 4.

DISCUSSION

The present study was made in order to describe vasoactive effects of Adm, as discovered during pilot experiments where a systemic i.a. bolus injection of Adm was used (Fig. 1). However, the results also give some information, although indirect, that may be relevant for predicting the rate and duration of i.a. Adm infusion that gives an optimal local Adm extraction fraction.

Vasoactive effects of adriamycin

The pilot experiments demonstrate how the vasoactive effect of Adm was discovered. As evident from the short half-time of blood Adm (Fig. 5) and as the washout curves followed a bolus injection, the curves must have been recorded during a rapidly declining blood Adm concentration. This may well have caused local flow changes, as suggested by change of washout curve slopes in only some of these experiments. Thus the pilot experiments are not readily comparable with the constant rate infusion experiments, where steady-state flow and pressure were established during Adm influence.

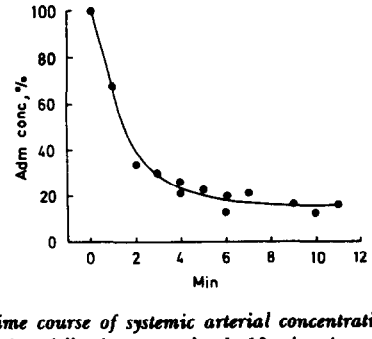

Fig. 5. Time course of systemic arterial concentration of [^{3}H]-*labelled Adm following completed* 10 min *i.a. infusion of* 0.6 mg/kg/min. *Normalised data: the* [^{3}H] *activity is expressed in % of peak value obtained during the last minute of the infusion period.*

A similar increase of AP occurred at similar Adm infusion rates during i.v. infusion and direct infusion into the renal blood stream (Figs 2 and 3). However, as the i.a. infusion gives a several times higher arterial Adm concentration to the kidney, this observation suggests an extrarenal origin of the systemic pressor response. This was confirmed by the experiments made with excluded renal circulation. Therefore the maximal increase of AP, obtained with about 0.3 mg/kg/min i.a. infusion, must imply a far from complete renal extraction of Adm, even at this low infusion rate.

An i.a. infusion of 1 mg/kg/min was equipotent to an i.v. infusion of 4–5 mg/kg/min in the sense that both gave a 60% reduction of LRBF (Figs 2 and 3). This strongly suggests a direct constrictor effect of Adm on renal resistance vessels, depending on the Adm concentration in renal arterial blood. If so, the systemic blood concentration must have declined to below pressor level during the 4-min recovery period (Fig. 4), indicating a blood clearance of Adm with a half-time of 2 min or less. This half-time agrees well with previous results [26–30] and is confirmed for the present type i.a. infusion by the results demonstrated in Fig. 5. It should be emphasised that this clearance probably reflects the phase of distribution between intra- and extra-vascular compartments rather than cellular uptake of Adm.

Neither the present data nor earlier literature seem to provide a clear answer as to how the vascular pressor effect of Adm is induced and mediated. However, the hypertensive effect observed is in contrast to the hypotensive effect of Adm in dogs, where histamine release appears to be involved [13].

In three of the four experiments with low Adm infusion rate (Fig. 2) tumour flow was found to increase, whereas intact tissue flow remained unaffected. This disparity may well be due to autoregulation in intact tissue, whereas the tumour vessels lack such ability. Thus tumour flow may have increased as a direct result of increased arterial pressure. This interpretation is in line with the relatively smaller reduction of tumour flow during the higher infusion rates (Fig. 2) which may reflect lack of vascular contractile elements and/or sympathetic innervation, as well as of sensitivity to circulating

vasoactive agents, as reviewed by Mattsson [31, 32].

Local extraction of adriamycin during local i.a. infusion

It is generally assumed that tissue uptake of Adm is flow-dependent, and a useful pharmacokinetic model in accord with this principle has been made [9]. This model is based on tissue Adm concentrations obtained several hours after a bolus injection. On the other hand, direct evidence of flow-dependent Adm uptake at a maintained high plasma concentration, as in the present experiments, does not exist.

The rationale of local i.a. administration of Adm is that tissue uptake dominantly depends on the plasma concentration. However, flow of the infused parent organ decides the i.a. infusion rate needed to maintain, and expose the tumour to, a certain plasma Adm concentration. For a given total dose this flow also limits the time of tumour exposure to a high Adm concentration.

A too high plasma concentration might oversaturate the capacity of the uptake mechanism and reduce local tissue extraction fraction for the total dose given. Hence local flow level as well as the concentration dependency of the Adm extraction ratio must be known before optimal infusion rate and duration can be predicted. Both the low renal extraction ratio at an i.a. infusion rate of about 0.3 mg/kg/min, as implied above, and the short half-time of blood Adm would suggest that a local i.a. bolus injection is not the best way to obtain a maximal local Adm extraction ratio.

Thus it seems clear that further studies are required in order to predict optimal local Adm uptake from a locally administered dose of adriamycin.

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