

Mechanisms Involved in the Adrenalin-Induced Blockade of Milk Ejection in Dairy Cattle¹ (42186)

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Abstract. To elucidate mechanisms by which epinephrine (epi) blocks milk ejection in cattle, blood serum oxytocin (OT) concentrations were measured in four heifers before, during, and after milking following either intrajugular injection of 0.85% saline (S) or epi (3 mg). S did not affect OT concentrations. They peaked 2 min after milking-machine attachment. OT declined 3 min after milking commenced, reaching resting concentrations 10-60 min after milking. Milk yields were not altered by S. Epi did not influence significantly basal OT concentration. Yet, OT released to milking appeared less than the saline control. Peak OT concentration after epi and milking was reached 1 min after machine attachment. OT declined within 3 min after milking commenced. Milk yield was reduced 48% after epi. Jugular vein and carotid arterial OT concentrations and mammary blood flow (MBF) were measured simultaneously in four multiparous cows. Blood was collected before, during, and after milking following S or epi (50 μ g). Jugular and carotid OT concentrations followed similar patterns for both treatments. Changes in carotid OT concentrations lagged behind those of the jugular vein by approximately 1 min. Elevated carotid OT concentrations were seen in two cows after milking and thought to be derived from nonhypothalamic-neurohypophysial sources. Epi (50 μ g) did not reduce blood OT concentrations, but reduced MBF by 95%. Milking induced increases in MBF seen in controls, were not observed with epi, and milk yield was reduced by 56%. Our experiments suggest that epi may inhibit OT release to milking stimuli at pharmacological doses. At lower doses, epi exerts its effects peripherally by acutely reducing MFB, thus preventing physiological concentrations of hormone from reaching the myoepithelium. An intrinsic action of epi on the myoepithelial cells of cattle is unlikely, but cannot be ruled out at this time. © 1985 Society for Experimental Biology and Medicine.

Over forty years ago, Ely and Petersen (1) subjected dairy cattle to frightful stimuli and intrajugular injections of adrenalin (epinephrine). These resulted in cessation of milk ejection and lowered milk yields. They proposed the theory that adrenalin caused "holding up of milk."

Various studies in the rat and rabbit have since suggested that milk ejection can be blocked by stress or epinephrine release via three mechanisms (2-5): (i) central inhibition of oxytocin release from the posterior pituitary, (ii) reduction of blood flow to the mammary gland, preventing physiological concentrations of oxytocin from reaching the myoep-

ithelium, and (iii) intrinsic action directly on myoepithelial β receptors.

The mechanism(s) whereby epinephrine blocks milk ejection in lactating cattle is far from clear. Sibaja and Schmidt (6) measured serum oxytocin (OT) concentrations of lactating cows by bioassay; before, during, and after milking and reported intrajugular injection of 3 mg epinephrine (epi) before or after udder washing inhibited OT release during milking and also blocked milk ejection. Their work also suggested that epi could reduce the efficiency of OT-induced milk ejection through its effects on myoepithelial cell β receptors. They attributed the blockade of milk ejection primarily to epi inhibiting OT release. This study was inconclusive for several reasons. The bioassay used to measure OT lacked sensitivity and was characterized by a high degree of variability (7). No attempt was made to measure effects of epi on mammary blood flow. Finally, the β blocker propranolol was added to the *in vitro* assay system and not ad-

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ministered to animals prior to epi injection. The biological actions of epinephrine may not be restricted to the myoepithelium of mammary parenchyma. Rat mammary parenchyma was used in the bioassay system to measure oxytocin. Epinephrine may influence milk removal *in vivo* by acting on smooth muscle cells located directly in the teat and/or myoepithelial cells within small milk ducts (8–10).

Recently, Lefcourt and Akers (11) examined effects of noradrenalin injection and infusion on radioimmunoassayable OT concentrations and milk yields of dairy cattle. Norepinephrine is the catecholamine which appears to be in highest concentration under resting conditions in cattle (11). Neither injection nor infusion of norepinephrine inhibited OT release in response to milking stimulation, even though milk yield was decreased by 8.6%.

The objective of our study was to elucidate further the mechanism(s) by which epinephrine blocks milk ejection in dairy cattle. In order to accomplish this, blood serum oxytocin concentrations were measured in heifers before, during, and after normal milking and before, during, and after milking following intrajugular epinephrine injection. In addition, jugular vein and carotid blood oxytocin concentrations, as well as mammary blood flow were measured simultaneously in multiparous cows before, during, and after normal milking and before, during, and after milking following epinephrine injection.

Materials and Methods. *Experiment I: Effects of epinephrine on oxytocin release and milk production of heifers.* Four pregnant lactating (100–120 days) Holstein heifers weighing from 450 to 475 kg were used to determine effects of epinephrine, injected prior to milking, on oxytocin release and milk production.

Animals were obtained from the Cornell University dairy herd and moved to stalls in an isolated monitor room on the farm. They were allowed 1 week of acclimation before experimentation. Heifers were fitted with indwelling jugular cannula 24 hr prior to experimentation (7). On the day following cannulation, 3 ml of 0.85% saline was administered to each animal intrajugularly 1 min before milking machine attachment. This served as the control. Premilking stimulation consisted of a 5–10 sec manual cleaning of the teats and

removing small amounts of milk (hand stripping). Twenty-four hr following saline administration, 3 ml epinephrine hydrochloride (1 mg/ml, Interstate Drug Exchange, Inc., Plainview, N.Y.) was administered as described for saline. Sibaja and Schmidt (6) reported that this dose of epinephrine ($\sim 6 \mu\text{g}/\text{kg}$ body wt) was sufficient in markedly reducing milk production in dairy cattle. Treatments were administered once. It was felt that at least two to four normal milkings would have been necessary for animals to readjust their production to preepinephrine treatment. We felt that repetitive injections of epinephrine at this pharmacological dose, to the same experimental animals, could potentially result in mastitis and future loss of milk production.

Blood samples were collected on both control and treatment days at -60 , -10 , -5 , 0 (milking machine attachment), and at five 1-min intervals during milking. Additional samples were taken 10 and 60 min after milking. Blood samples were kept at 4°C for 24 hr. Sera were harvested by centrifuging blood at $1000g$ for 30 min and were stored at -20°C until assayed for oxytocin. Oxytocin was measured in sera by the radioimmunoassay method of Gorewit (7) as modified by Wachs and Gorewit (12).

Animals were milked at 0800 and 2000 hr. End of milking was determined by the milker. Milk yields were determined by weighing the milk bucket after milking and subtracting from it the weight of the empty bucket.

Experiment II: Effects of epinephrine on oxytocin release, mammary blood flow, and milk production of multiparous cows. To further clarify the role of epinephrine blockade on milk ejection, four late lactating (200–250 days) nonpregnant Holstein cows weighing from 589 to 595 kg and ranging from 4 to 5 years of age were used. Animals were moved to an environmentally controlled monitor room 10 days prior to experimentation. Cows were surgically fitted with 12- or 16-mm ultrasonic transit-time blood flow probes (Transonic Systems, Ithaca, N.Y.) on the right external pudic artery as well as cannulae in the right jugular vein and right carotid artery as described by Gorewit *et al.* (13).

After a 3-day postoperative recovery period, blood samples were collected simultaneously from the right carotid artery and right jugular

vein at -60, -30, -10, -5, -1, .5, 0 (attachment of milking machine) at 1-min intervals for 15 min and at 20, 30, and 60 min. This sampling scheme was repeated for six consecutive control milkings after saline injection and six consecutive milkings after epinephrine injection. Blood handling and harvesting of sera were as described in Experiment I. Pre-milking udder massage was as described for Experiment I. The blood flow meter was interfaced to a computer which allowed for automated sampling every 0.5 sec. Measurements were stored on diskettes for later analyses.

One minute prior to milking, 0.75 ml of 0.85% saline or 0.75 ml of epinephrine (50 μ g, Interstate Drug Exchange, Inc.) was injected into the right jugular vein. The injection occurred before any manipulation of the udder or milking. The 50- μ g dose of epinephrine (~80 ng/kg body wt) used was over a thousand times less than that used by Sibaja and Schmidt (6), and the dose of epinephrine used in Experiment I described earlier. We felt this level of epinephrine was more representative of physiological doses of the hormone reached during exposure to stressful stimuli (11). This dose of epinephrine was also shown previously to reduce mammary blood flow in cows by as much as 90% (13).

Cows were milked a second time, 30 min after the last blood sample was taken after each primary milking following epinephrine. This was necessary to remove that quantity of milk which was not effectively harvested as a result of the epinephrine injections.

Statistical analyses. Significance of treatments on oxytocin release, blood flow, and milk yield were tested using ANOVA procedures (14). Areas under each peak, representing changes in arterial and venous oxytocin concentrations postmilking, were measured using a digital planimeter. Means for these areas (responses) were compared for significant differences using a Student's *t* test (15).

Results. *Experiment I: Effects of epinephrine on oxytocin release and milk production of heifers. Oxytocin release.* Figure 1 illustrates mean oxytocin concentrations for heifers given saline and 3 mg epinephrine prior to milking. The average basal concentration of oxytocin before saline administration was 7.8 ± 0.14

μ U/ml (mean \pm SE). Saline did not appear to affect the milking-induced rise in oxytocin. Average peak oxytocin concentration after saline and milking was $31.4 \pm 10.0 \mu$ U/ml and was reached 2 min after milking machine attachment. Oxytocin declined within 3 min after milking commenced. Basal oxytocin concentrations were reached between 10 and 60 min after milking. The average basal oxytocin concentration in sera before intrajugular epinephrine injection was $8.0 \pm 0.82 \mu$ U/ml (Fig. 1). The average peak oxytocin concentration after epinephrine and milking was $17.0 \pm 2.6 \mu$ U/ml and was reached 1 min after milking machine attachment. Oxytocin declined to $12.7 \pm 2.1 \mu$ U/ml within 3 min after commencement of milking (Fig. 1). Basal concentrations of oxytocin were reached by 10 min after milking commenced.

Milk production. The average milk yield of animals after saline injection was 11.0 ± 0.77 kg. Yield did not appear to be influenced by saline injection (Fig. 2). However, the average milk yield for heifers after epinephrine was 5.7 ± 0.99 kg and was significantly ($P < 0.05$) reduced 48% when compared to milk yields after saline (Fig. 2).

Experiment II: Effects of epinephrine on oxytocin release, mammary blood flow, and milk production of multiparous cows. Normal milkings. Figure 3 illustrates relationships between mean jugular vein and carotid arterial oxytocin concentrations and mammary blood flow (MBF) before, during, and after milking following intrajugular S injection.

Jugular vein OT concentrations averaged 20 μ U/ml prior to milking. Jugular vein concentrations rose to an initial peak of $47 \pm 3.0 \mu$ U/ml (means \pm SE) at 2 min after milking machine attachment. Oxytocin levels fell to $43 \pm 1.0 \mu$ U/ml at 3 min, rose once again at 4 min ($44 \pm 0.86 \mu$ U/ml), and slowly fell to baseline by 14 min post machine attachment.

Carotid arterial OT concentrations followed patterns similar to those of the jugular vein. Carotid arterial OT concentrations averaged 21 μ U/ml prior to milking (Fig. 3). Carotid concentrations rose to an initial peak of $38 \pm 1.2 \mu$ U/ml at 3 min after milking machine attachment. Oxytocin levels fell up to 5 min, slowly falling to baseline concentrations 8 min after machine attachment. In addition to the increases in serum oxytocin during milking,

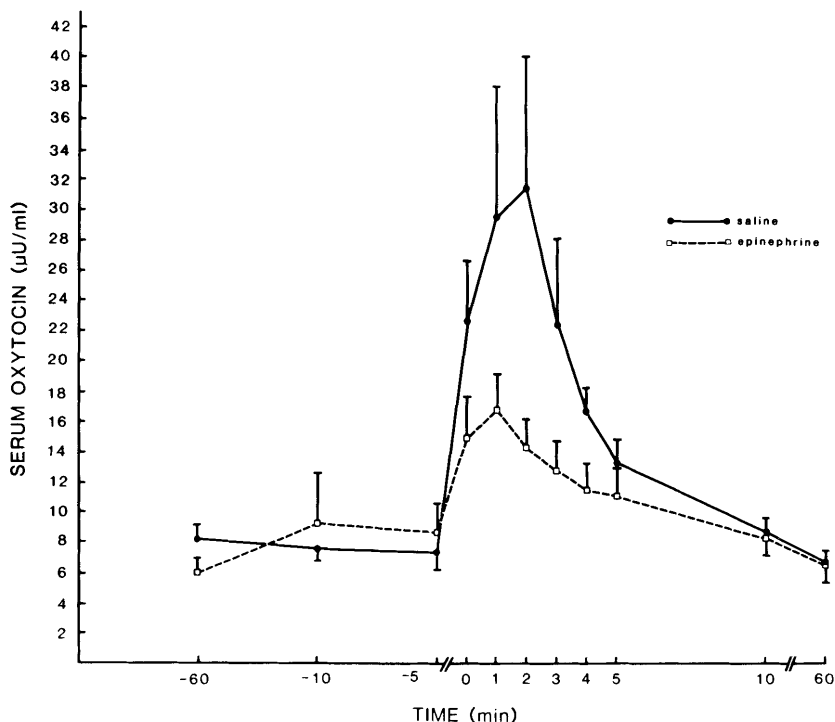


FIG. 1. Mean concentrations of oxytocin for four heifers given a saline injection or 3 mg epinephrine hydrochloride into the jugular vein 1 min prior to milking stimuli. Attachment of the milking machine occurred at 0 time.

two cows displayed elevated carotid arterial oxytocin concentrations during three out of the six control milkings at 11 and 15 min post milking machine attachment. Corresponding increases of jugular vein oxytocin were not seen (Fig. 3). Areas under oxytocin milking response curves for jugular and carotid samples (-60 to +10) were not significantly different.

Mammary blood flow averaged 1.02 liters/min prior to milking and saline injection (Fig. 3). A 51% increase in flow was seen during milking. Peak flow ($2.1 \pm .2$ liters/min) was seen 4 min from commencement of milking. Increased MBF was associated closely with milking-induced changes in oxytocin concentrations in both the jugular vein and carotid artery. Blood flow reached baseline levels by 8 min post machine attachment (Fig. 3).

Control milkings after saline did not appear to influence milk yields (Fig. 4). Milk yields averaged 7.2 kg.

Epinephrine treatment. Epinephrine injection did not influence either jugular or carotid

concentrations of oxytocin released during milking (Fig. 5). Once again, changes in OT release patterns prior to and during milking were similar for both blood vessels. Jugular vein concentrations averaged $25 \mu\text{U/ml}$ prior

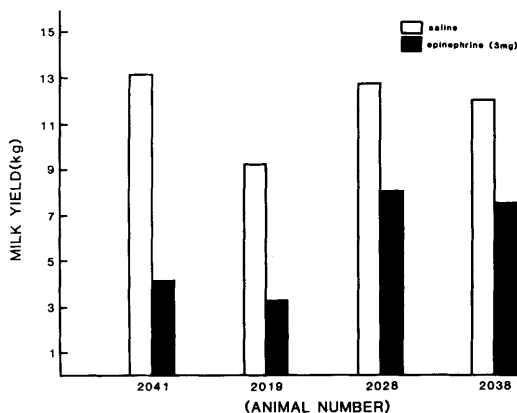


FIG. 2. Average milk yields for four heifers given a saline or 3 mg epinephrine hydrochloride injection into the jugular vein 1 min prior to milking stimuli.

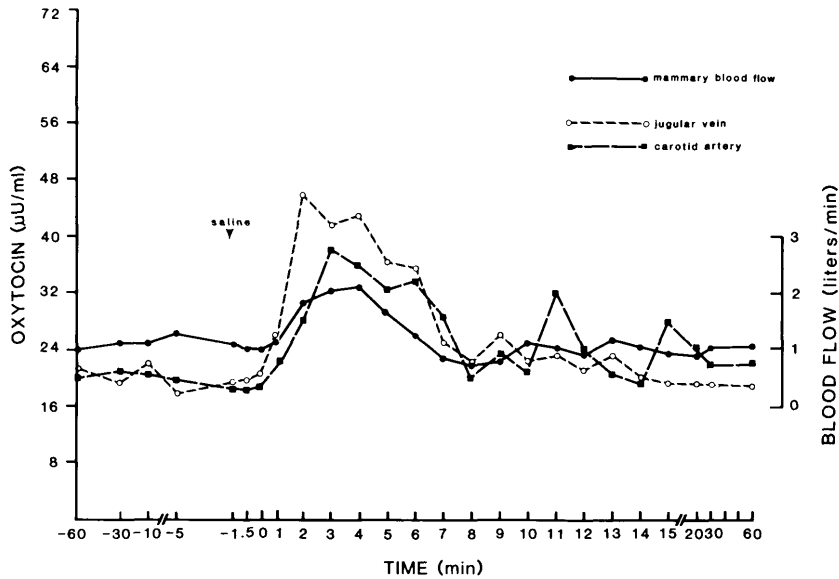


FIG. 3. Relationships between mean jugular vein and carotid arterial oxytocin concentrations and mean mammary blood flow of cows before, during, and after six milkings following saline injection. Attachment of the milking machine occurred at 0 min. Saline was injected into the jugular vein at -1 min. Each point on the blood flow curve represents an average of 120 readings taken over an interval of 1 min.

to milking. Jugular vein oxytocin rose to $46 \pm 6.2 \mu\text{U/ml}$ 2 min after milking machine attachment. Oxytocin fell at 3 min after machine attachment to $40 \pm 3.0 \mu\text{U/ml}$ and rose to $47 \pm 3.2 \mu\text{U/ml}$ 4 min post machine attachment (Fig. 5). Baseline levels were reached by 12 min after commencement of milking. Carotid arterial oxytocin concentrations averaged 23

$\mu\text{U/ml}$ prior to epinephrine and milking (Fig. 5). A peak in oxytocin of $45 \pm 1.2 \mu\text{U/ml}$ was seen 3 min after machine attachment. Levels of oxytocin fell at 4 min post milking, rose slightly at 5 min, and did not reach baseline by 60 min post milking machine attachment.

Elevated oxytocin concentrations in carotid arterial samples were seen at 13 and at 60 min

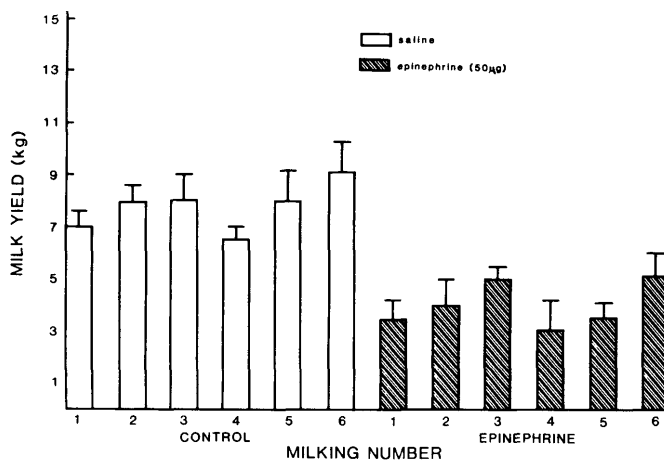


FIG. 4. Average milk yields of four cows \pm SE after normal milking and after 50 μg of epinephrine and milking.

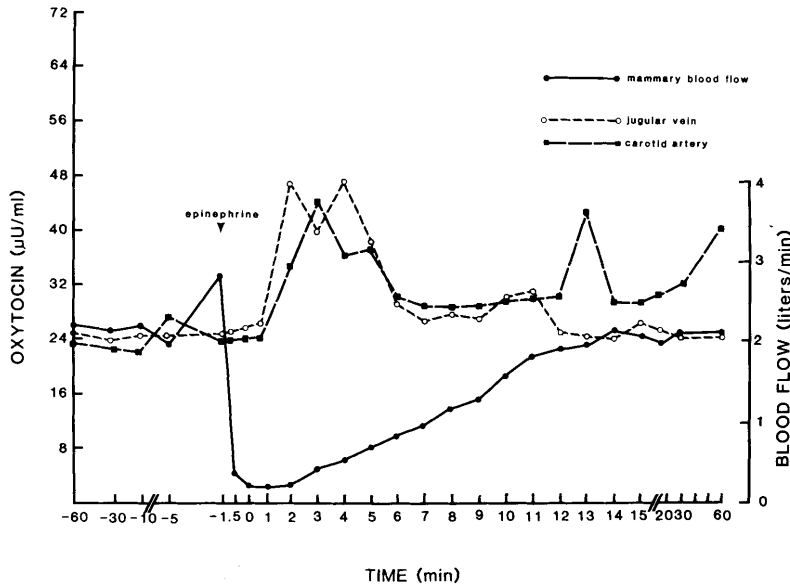


FIG. 5. Relationships between mean jugular vein and carotid arterial oxytocin concentrations and mammary blood flow of cows before, during, and after milking, following 50 μg of epinephrine. Epinephrine was injected into the jugular vein before milking stimuli (-1 min). Attachment of the milking machine occurred at 0 min. Each point on the blood flow curve represents an average of 120 readings taken over an interval of 1 min.

after commencement of milking in the same two cows showing elevated levels after saline injection and milking. These peaks in oxytocin were observed in four of six milkings after epi. Elevated oxytocin concentrations were not seen in corresponding samples taken from the jugular vein. There were no significant differences in oxytocin concentrations as a result of epi treatment. Moreover, areas under oxytocin milking response curves for jugular and carotid samples (-60 to +10 min) were not significantly different.

Mammary blood flow averaged 2.0 liters/min and increased 26% with respect to rest immediately upon epinephrine injection. Mammary blood flow decreased precipitously within 30 sec (Fig. 5). Blood flow to the udder decreased 95% by 1 min post injection (Fig. 5). Blood flow remained low for approximately 3 min after injection. The abrupt milking-induced rise in MBF observed after saline injection was not seen. Mammary blood flow rose slowly during milking. Resting MBF was not reached until 14-15 min post milking machine attachment.

Epinephrine given 1 min prior to milking significantly ($P < 0.05$) reduced milk yield

from an average of 8.0 to 3.5 kg (Fig. 4). This amounted to a 56% decrease in milk yield.

Discussion. *Experiment 1: Effects of epinephrine on oxytocin release and milk production of heifers.* Basal oxytocin concentrations measured during rest and during milking in this experiment were similar to those reported by Gorewit (7) and Wachs *et al.* (12).

Epinephrine administration appeared to affect the milking induced rise in serum oxytocin when mean concentrations were graphically compared with those after saline treatment (Fig. 1). However, differences between the total amount of oxytocin released during -5 to +60 min for saline and epinephrine treatment were not significant. A broad range of peak oxytocin concentrations was observed for animals after milking stimulation, after both saline and epinephrine treatments. Variation was due to animal differences with regard to the time taken for the reflex release of oxytocin to premilking and milking stimuli and the fact that some animals released more oxytocin than others.

Sibaja and Schmidt (6) reported similar results. Concentrations of oxytocin in cows, when 3 mg epinephrine was injected intrajugularly either before or after udder stimulation,

were significantly lower than those during normal milking. The significant depression in milk yield after 3 mg epinephrine, in our study, was similar to that reported by Sibaja and Schmidt (6).

Experiment II: Effects of epinephrine on oxytocin release, mammary blood flow, and milk production of multiparous cows. The pattern of oxytocin release into the jugular vein throughout milking has been described previously (6, 7, 12, 16). However, few if any reports exist comparing carotid arterial and jugular vein oxytocin concentrations prior to and throughout milking. Our data show the close relationship between oxytocin concentrations in jugular venous and carotid arterial blood. Changes in carotid arterial oxytocin concentrations may be used to monitor physiological events in cattle such as milk ejection. However, blood passing through the carotid artery is more likely to contain metabolites of oxytocin, since it has passed previously through organs which metabolize it.

Non-hypothalamic-neurohypophysial sources of oxytocin have been reported recently (17-20). The hormone has been localized by immunological, and biochemical techniques in the ovary (17-20), and placenta (18) of various animal species. The elevated carotid arterial oxytocin concentrations observed post milking in two of the four cows used in our studies may have been derived from the ovaries.

Epinephrine injection did not influence significantly either jugular or carotid arterial oxytocin concentrations which is consistent with results shown in Experiment I and the studies of Lefcourt and Akers (11) using noradrenalin.

Blood flow responses to normal milking following saline in our experiment were similar to those described in other studies. For example, Reynolds *et al.* (21) reported that udder massage of goats increased blood flow 30-50% above control rates in conscious and anesthetized animals. These changes were measured using an electromagnetic flow probe around the external pudic artery.

Houvenaghel *et al.* (22) implanted electromagnetic flow probes around the external pudic artery of lactating cows. They examined influences of hand milking, udder massage and oxytocin injection on glandular blood flow.

Hand milking resulted in a distinct blood flow increase through the mammary artery. After a mean latency of 50 sec (11-93 sec), flow began rising slowly but progressively. At the moment of milk ejection, blood flow curves showed an abrupt upward swing. Flow became stabilized at an increased level persisting over the whole milking period. At the end of milking, flow curves returned to their control values within 30 to 70 sec. This was a 90 to 300% increase in flow during diastole, as compared to the control level. They found that milk ejection occurred 47 to 130 sec after the onset of milking.

Gorewit *et al.* (23) showed that cows in late lactation had mammary blood flow rates of 1.23 to 2.3 liters/min using a transit time blood flow meter. Blood flow increased within 42 ± 4.3 sec (mean \pm SE) from machine attachment. The mean percentage increase in blood flow averaged 28.9 ± 2.9 (mean \pm SE). Resting blood flow was achieved by 4.6 ± 0.19 min after machine attachment.

It has been over three decades since Hebb and Linzell (24) described the vasoactive effects of epinephrine on mammary gland blood flow in perfused goat mammary glands. Recently, Gorewit *et al.* (13) studied response patterns for mammary blood flow and carotid arterial blood pressure after a $50 \mu\text{g}$ intrajugular injection of epinephrine. Just after epinephrine injection, carotid arterial blood pressure rose from an average of 140 ± 5 to 215 ± 15 mm Hg (mean \pm SE). The carotid arterial pressure response to epinephrine paralleled an increase in mammary blood flow. The latency of the increase was approximately 30 sec. A precipitous drop in arterial blood flow to the udder was seen as in Experiment II of our present study. The depression in blood flow to the udder ranged from 90 to 100% and lasted about 15 min. Dhondt *et al.* (25) and Houvenaghel (26) showed similar results using 1 to $500 \mu\text{g}$ of various vasoactive agents including epinephrine and electromagnetic blood flow techniques.

It appears that 3 mg of epinephrine when injected into the jugular vein decreases the amount of oxytocin released in response to milking stimuli. Milk yields are also lowered. Intrajugular injection of $50 \mu\text{g}$ of epinephrine significantly reduces milk yields, but does not significantly reduce the milking-induced re-

lease of oxytocin. We hypothesize that the initial rise in blood flow to the udder, upon 50 μ g epinephrine injection, is caused by an instantaneous baroreceptor reflex. Epinephrine's inotropic effect on the heart increases cardiac output, therefore, arterial pressure rises (27). The carotid sinus and aortic arch baroreceptors sense the elevated arterial pressure which increases their rate of signal transmission to reduce sympathetic tone and enhance the parasympathetic tone. This vagally mediated response results in peripheral vasodilation specifically noted at the mammary artery by an increase in blood flow. The vasoconstrictor properties (α receptor) would predominate next to selectively lower mammary blood flow.

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