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Chronic Ureteric Obstruction and its Impact on the Coordinating Mechanisms of Peristalsis (Pyeloureteric Pacemaker System)

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Summary. We present the results of a study designed to characterise urine transport in the healthy and chronically obstructed upper urinary tract. Fifteen healthy and 11 hydronephrotic pigs were used; experimental hydronephrosis was produced by partially obstructing the ureter. Data consisting of the peristaltic rate, bolus volume, and the urine flow rate were collected and related to varying increments of diuresis. The transmission characteristics of renal pelvic to ureteric contractions were studied by extracellular electrodes. Similarly, in hydronephrotic preparations we studied the transmission between the proximal and middle pelvis to the ureter. In healthy preparations, the contraction frequency of the renal pelvis and the ureter is identical, while in obstructive cases, the contraction frequency of the upper pelvis is not coordinated with the lower pelvis or ureter. While diuresis increased bolus volume to a maximum of 1,200% in the healthy and 660% in the hydronephrotic kidney, the peristaltic rate changed by only 45% and 50% respectively. The results of this study show that chronic ureteric obstruction alters the coordination of ureteric peristalsis and thereby disrupts the pacemaker mechanisms of the renal pelvis.

Key words: Pyeloureteric Pacemaker, Diuresis, Obstruction, Peristaltic Coordination.

Introduction

This study is concerned with effects of chronic partial ureteric obstruction on transmission characteristics in the pelvis and ureter of the multicalyceal kidney of the pig. The regulation of ureteric peristalsis and bolus volume by diuresis was assessed in both healthy and obstructed preparations. Previous investigations have been carried out in the unicalyceal system [8] or have examined only restricted ranges of diurectic levels [5–7]. The present study was performed under dynamic changes of diuresis covering a broad spectrum of urine flow rates. In order to establish the pelvicalyceal pacemaker system's control of urine transport from the renal pelvis to the lower urinary tract, particular emphasis has been placed upon the characterisation of the coordination of ureteric peristalsis. In this way, the mechanisms of pacemaker regulation in the hydronephrotic kidney are compared to the function of the healthy urinary tract.

Methods

Healthy Preparations

Fifteen pigs weighing between 20–30 kg were anaesthetised with 2% Halothane and 98% O_2. The upper urinary tract was exposed and a pair of extracellular electrodes were implanted in the renal pelvis and the ureter. The ureter was drained via a #5 F feeding tube for the measurement of bolus volume. Recordings of the electrical activity of pelvis and ureter were made simultaneously with bolus volume on a high frequency response UV polygraph. An intravenous catheter was passed via an ear vein for the administration of fluids and mannitol. Recordings were made at the lowest possible urine flow rate with an intravenous infusion of approximately 1.0 ml/min for a 10 min control period. Subsequent intravenous doses of 5, 10, 20 and 50 ml of mannitol 25% were given at 10 min intervals to increase the level of diuresis. Following the 50 ml mannitol dose, data were recorded for an additional 20 min period. The same kidney used for the above measurements was subsequently chronically obstructed and used for both control and occlusion studies. The contralateral kidney was left undisturbed.

Hydronephrotic Preparations

A partial obstruction was made by constructing a tunnel in the psoas and embedding the proximal 1/3 of the ureter. The pig was then closed and allowed to recover, and the onset of hydronephrosis was then monitored with intravenous pyelograms. Following an 8 to 10 week period of obstruction, the 11 surviving pigs were anaesthetised in the same manner as outlined above and the upper urinary tract exposed. This time, extracellular electrodes were placed at the most proximal regions of the renal pelvis, mid pelvis, and the ureter, distal to the obstruction. The diurectic protocol was then repeated.

Data Analysis

The principal parameters measured in the controls were: renal pelvic and ureteric frequency, percentage transmission from pelvis to ure-

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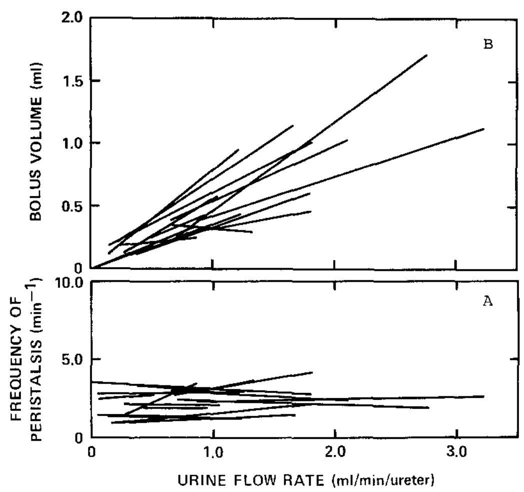

Fig. 1. **(A)** Variation of uteric peristaltic frequency with respect to flow rate demonstrating that the peristalsis occurs within the range of 2–5/min^{-1} while urine flow ranges from 0.01 to over 3.0/ ml/min/ureter. **(B)** Regression equations relating urine flow rate to measured bolus volume showing the range of bolus volume values which can be obtained in relation to diuretic stimuli. It is shown that the general tendency is for the bolus volume to increase as the urine flow rate increases

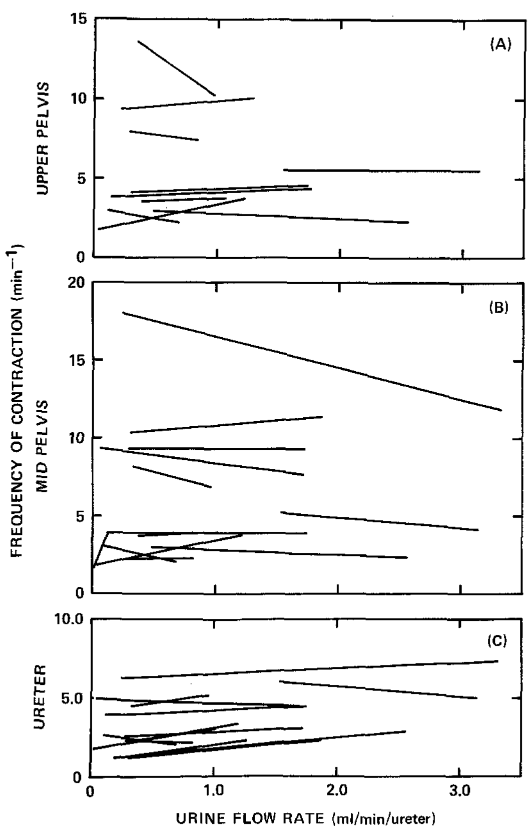

Fig. 2. Effect of chronic obstruction on the contractile frequency of the proximal and distal parts of the renal pelvis and of the ureter. It is shown that much higher frequencies occur in the proximal regions of the pelvis compared to the ureter. Ureteric contractions in the chronically obstructed upper urinary tract are higher than those of the healthy pyeloureters

ter, bolus volume, and urine flow rate. These quantities were measured for each 10 min period and a regression line was computed relating to the peristaltic rate (P), to bolus volume (B), and urine flow rate (F). The percentage increase in peristaltic rate, bolus volume and urine flow rate was also computed from the baseline values obtained during each control period. Finally, a multiple regression analysis was made relating $B = K_1 + K_2F + K_3P$. K_1, K_2, and K_3 are constants. In hydronephrotic preparations where the transmission of contraction was not uniform, the percentage transmission between upper pelvis to mid pelvis, and from mid pelvis to ureter, was calculated for each 10 min period of recording. A regression line for each experimental preparation was subsequently calculated, evaluating percentage transmission from each region as a function of flow rate. A cumulative regression equation for each set of equations was computed and the 95% confidence interval was calculated. The individual regression equations and the overall regression equations were plotted using a digital plotter. The 95% confidence interval was also plotted on the same axis from the equation (12–34) given in [13].

Results

Peristaltic Frequency and Urine Flow Rate

The mean frequency of peristalsis in control preparations varied from zero to four contractions per min over a variation of urine flow rates between 0.01 and 3.5 ml/min/ureter. Within the dynamic range of urine flow rates studied there was little individual variation in mean peristaltic frequency, as can be seen from the individual regression lines of the 15 healthy pigs (Fig. 1A). The overall regression equation relating the frequency of peristalsis with flow rate in all preparations is given by $P = 2.04 + 0.28$ F. Figure 1B illustrates a number of linear regression equations relating urine flow rate and bolus volume, and also shows the range of bolus volume which can be obtained with respect to the given diuretic stimulus. The overall regression equation is given by $B = 0.01 + 0.40$ F, indicating that the general tendency in these preparations is for the bolus volume to increase as the urine flow rate increases.

Similarly, Fig. 2 illustrates the variation of upper pelvis, mid pelvis and peristaltic rate with urine flow rate in 14 hydronephrotic kidneys. The individual regression equations indicated by Fig. 2 show an overall higher mean frequency of peristalsis in hydronephrosis than in unobstructed pyeloureters.

In healthy pyeloureters, ureteric contractions, once initiated from the proximal regions of the renal pelvis, were propagated throughout the entire length of the ureter. However, in hydronephrotic pyeloureters, contractions originating at the most proximal regions of the pelvis were not propagated throughout the ureter. The individual regression equations for urine flow rate and the contraction frequency in the upper pelvis are illustrated in Fig. 2A and those in the middle pelvis in Fig. 2B.

The transmission properties of renal pelvic contractions from the upper to middle pelvis and mid pelvis to the ureter are illustrated in Fig. 3. As indicated by Fig. 3, the transmission from the upper pelvis to the mid pelvis was highest, approximately 88%, while that from the middle pelvis to ureter was approximately 70%. Transmission within the renal pelvis to the ureter did not significantly improve with urine flow rate. The overall regression equation for the percentage transmission between upper and mid pelvis and flow rate is given by $T = 87.73–0.00$ F. Similarly, the equation for that between middle pelvis and ureter is $T = 70.05 + 0.33$ F.

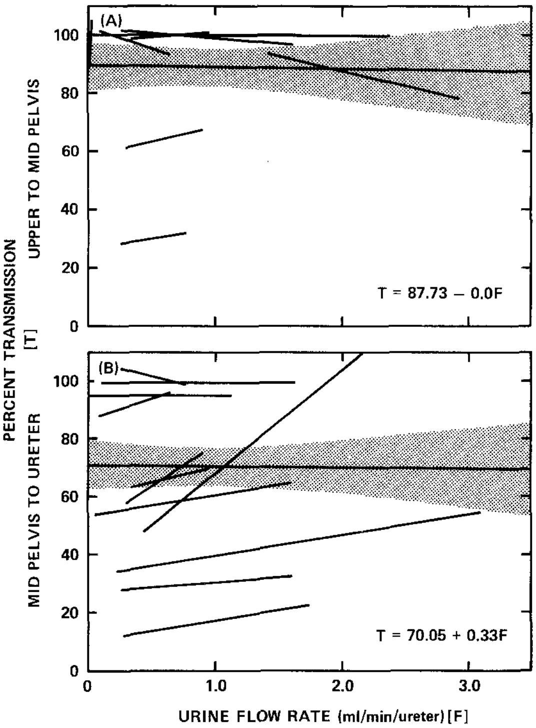

Fig. 3. Loss of transmission between the renal pelvis and the ureter. Transmission is highest between upper pelvis to middle pelvis compared with middle pelvis to ureter. Normalized values of percentage of contraction transmitted from each region are shown. The shaded line gives the 95% confidence limit for the regression equations shown

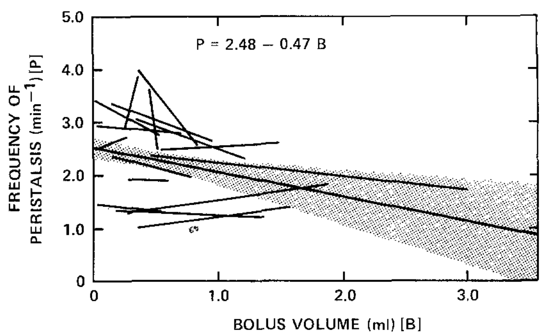

Fig. 4. Peristaltic variation with respect to bolus volume showing that with increasing frequency of contraction the overall tendency is for the bolus to decrease

Peristaltic Frequency and Bolus Volume

The bolus volume in healthy preparations ranged from 0.00 to 3.4 ml. Figure 4 illustrates the individual regression lines relating peristaltic frequency and bolus volume in the 15 pigs studied. The overall regression equation is given by $P = 2.48 - 0.47$ B.

Increasing diuretic stimuli produced a significant increase in the size of the bolus propagated by the ureter in both the control and hydronephrotic kidneys.

The percentage increase from baseline conditions in bolus volume, peristaltic frequency, and flow rate is illustrated in Fig. 5. Together, the results illustrated in Fig. 5 show that accommodation to diuresis is accomplished by a greater percentage increase in the size of the bolus than in peristaltic frequency.

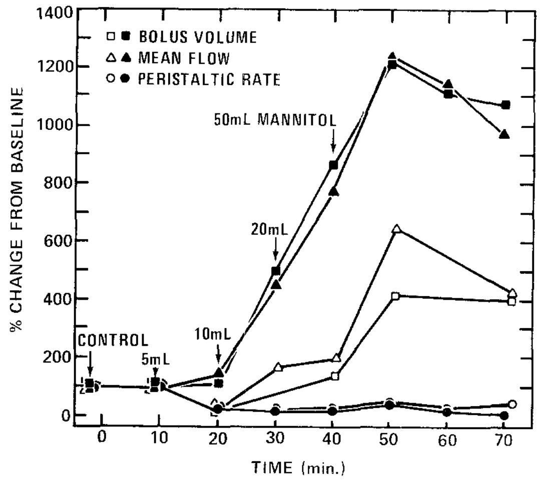

Fig. 5. Comparison of the percentage increase from control values in (a) bolus volume, (b) mean urine flow rate, and (c) peristaltic rate, to diuretic stimuli between healthy and chronically obstructed upper urinary tracts. Filled symbols represent the healthy, and empty symbols represent the obstructed preparations. It is shown that the maximum increase in peristaltic rate is minimal with increasing diuretic stimuli. Bolus volume and urine flow rate increase proportionately with the diuretic stimulus

Discussion

This study demonstrates that chronic partial ureteric obstruction alters both the frequency of peristaltic contractions and the transmission of contractions within the renal pelvis and ureter. It is evident that much higher frequencies occur in the proximal regions of the pelvis in the obstructed system. It is also shown that loss of transmission between the distal part of the renal pelvis and the ureter is characteristic of chronic obstruction.

Previously, it has been shown that in the healthy unicalyceal [1] and [9] pyeloureter, ureteric peristalsis is controlled by the proximal part of the system. In the multicalyceal kidney, pelvic contractions are propagated to the ureter without interruption once they are initiated. At low flow rates, the pelvis accumulates urine over a comparatively long period before the formation of a bolus and the propagation of peristaltic contractions. During this collection phase the pelvic pressure is comparatively low. While contracting, the pelvic pressure increases to a maximum, whereupon ureteric peristalsis is initiated. In vitro studies have demonstrated [9] that the stimulus for this pelvic contraction usually originates in the calyceal system. Based upon simultaneous calyceal and renal pelvic recordings [14], it was shown that during renal pelvic contractions the calyceal pressures remain comparatively low, and, in fact, the calyces are hydraulically isolated from the pelvis.

Under conditions in which urine flow rate is increased from low to high levels by a diuretic stimulus, the rate of peristalsis reaches a maximum frequency of approximately 6 per min. At maximum frequencies further increase in fluid flow is accommodated by an increase in the bolus volume. At extremely high urine flow rates, ureteric contractions occur at the same frequency as that of the calyces. These findings support the concept of a calyceal pacemaker system which is responsible for initiating renal pelvic contractions. Anatomical evidence for such a pacemaker system has also been described by Gosling et al. [10]. In this context, in vitro studies have shown that the initiation of coordinated renal pelvic contractions are independent of distension forces.

An alternative theory has been proposed which suggests that the upper urinary tract is a bi-stable system which responds directly to distentions, thereby denying the existence of an active pacemaker system. In this hypothesis, ureteric contractions occur in response to the accumulation of fluid within the renal pelvis. In such a system, bolus volume would be expected to remain relatively constant, so that increased fluid flow during diuresis would be accommodated by a rise in peristaltic rate. As seen from the above, the available evidence does not support this hypothesis, and furthermore, data relating frequency of peristalsis to urine flow rate fails to support this alternate concept.

In summary, urine transport in the healthy upper urinary tract appears to be regulated by a hierarchical sequence in which the highest inherent frequency occurs within the calyceal system. In the renal pelvis a gradient exists such that the regions with higher frequencies are located in the most proximal regions of the pelvis. Such a gradient has been shown in the unicalyceal system [3, 12].

It is evident from this study that obstruction and the ensuing hydronephrosis alter the hierarchical order of pacemaker function within the urinary tract. Such disruption causes discoordination of pelvic contractility, resulting in incomplete emptying of the pelvis. Thus, residual pelvic urine contributes to further dilation of the upper urinary tract. Also, it is apparent that chronic obstruction disrupts the coordination mechanism of the proximal and distal parts of the renal pelvis. The result is that the proximal regions of the pelvis are dissociated from the distal pelvis and ureter. During increased flow, the contractile rate of the proximal pelvis is increased, while the distal part is maintained at a lower frequency. Since ureteric peristalsis and the associated bolus volume are in phase and of the same frequency as the electrical activity of the distal pelvis, the latter can be considered as the region which paces ureteric activity. Thus, it seems that the net effect of chronic obstruction is the loss of electrical conduction through the renal pelvic wall.

Hydrostatic pressures within the renal pelvis differ in the chronically obstructed upper urinary tract from those in the intact system in that (a) the resting level hydrostatic pressures are higher in the former and (b) intrapelvic pressure changes associated with electrical activity are absent in the obstructed renal pelvis. Two possible explanations may account for these observations: (1) either the obstructed renal pelvis is unable to generate coordinated contraction waves, or (2) distension pressures are insufficient to initiate a propagated impulse. However, as pelvic distension increases following acute total obstruction [11], the system changes so that electrical and pressure events in the wall of the pelvis become coordinated. The first possibility may also be extended to explain other phenomena observed in the obstructed renal pelvis. Thus, in the context of a multiple coupled pacemaker system controlling ureteric peristalsis, obstruction to outflow and subsequent distension of the renal pelvis may contribute towards structural disruption of renal pelvic smooth muscle. Specific morphological evidence of this disruption has been provided recently [11]. The consequences of these anatomical changes may also account for the loss of electrical coupling between multiple pacemaking regions. Consequently, it may be that fundamental alteration in the regulatory process of urine transport in the obstructed system is the loss of hierarchical organisation of the multiple coupled pacemakers within the renal calyces and pelvis. This deficit is manifested by the lack of regional coordination in renal pelvic activity; this results in a net increase in the resting value of renal pelvic pressures and an absence of effective contractions. The degree of disruption may depend upon the severity and duration of the obstructive process.

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