# Effect of Fenoldopam on Renal Function Following Nephrotomy in Normal Dogs

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**(ABSTRACT)**

**Objective:** To evaluate the effect of fenoldopam on renal function in normal dogs subjected to bisection nephrotomy. In addition, effects of bisection nephrotomy on renal function in normal dogs were evaluated.

**Study Design:** Controlled, randomized, blinded experiment

**Sample Population:** Sixteen mixed breed adult dogs

**Methods:** Dogs were paired for sex, body weight, and approximate age and were assigned to one of two groups: fenoldopam (F) or placebo (P). Baseline glomerular filtration rate (GFR), blood urea nitrogen (BUN), serum creatinine (SCr), urinalysis (UA), and urine culture were performed prior to surgery. A left bisection nephrotomy was performed via a standard midline celiotomy. Dogs in Group F received perioperative intravenous infusion of fenoldopam (0.1 μg/kg/min) for 90 minutes; dogs in Group P received 0.9 % saline (equivalent volume/kg) for 90 minutes. Body temperature, heart rate, respiration, direct arterial blood pressure, and urine volume were recorded during

anesthesia. Renal function was assessed by measuring SCr, BUN, and GFR based on quantitative renal scintigraphy using $^{99m}$Tc-DTPA at 1, 21, and 42 days after surgery.

**Results:** There was no significant difference between groups in physiologic parameters assessed. There was no significant difference in GFR, BUN, or SCr between groups or between operated or control kidneys.

**Conclusions:** Bisection nephrotomy in normal dogs with renal arterial occlusion of 15 minutes and a simple continuous capsular closure does not adversely affect renal function.

**Clinical Relevance:** Further study investigating perioperative effects of fenoldopam in dogs with existing renal dysfunction is indicated. Bisection nephrotomy, as described in this study, does not decrease renal function as measured by BUN, SCr, or GFR.

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## Introduction

### *History of Nephrotomy*

Nephrotomy is a surgical incision made into the renal parenchyma.[1] The idea of renal surgery probably originated with Hippocrates, although it is not known if he ever actually performed renal surgery. Celsus considered any renal wounds to be uniformly fatal, and Galen did not consider surgery appropriate for renal calculi. In the 14th century, renal surgery was considered an "audacious act" that was "highly dangerous and usually fatal". There were various reports of renal surgery throughout the centuries, but no solid evidence of a successful nephrotomy was recorded until the late 1800s.[2]

With the advent of radiography as a diagnostic tool for renal calculi in 1895, nephrotomy for removal of nephroliths became more common. Disadvantages of nephrotomy were also clearly recognized, and several prominent authors described morphological changes observed in kidneys following nephrotomy. Injury caused by incising the kidney appeared to be minor compared to damage caused by trying to control hemorrhage and repair the wound. Although methods to quantitate functional change were fairly insensitive, it was noted there was a decline in renal function following nephrotomy.[2]

***Anatomy***

Canine kidneys are paired structures lying against sublumbar muscles on either side of the vertebral column. Both kidneys are retroperitoneal with one surface in contact with sublumbar muscles and the other covered by peritoneum. Based on normal position, each kidney has cranial and caudal poles, medial and lateral borders, and dorsal and ventral surfaces. The lateral border is convex and the medial border is indented to form the hilus. Major structures (arteries, veins, lymphatics, ureter) enter and leave the kidney through the hilus. The right kidney is more firmly attached to the dorsal body wall, is slightly cranial to the left kidney, and contacts the caudate lobe of the liver. Both kidneys are covered by a fibrous capsule, surrounded by adipose tissue, and held in position by subperitoneal connective tissue. Kidneys are not fixed in the abdomen and may move during respiration or with movement of viscera. [3] The kidney is organized into an outer cortex and inner medulla, and the medulla unites to form a single papilla which projects into the renal pelvis. The pelvis is a dilated portion of the ureter located within the kidney. [4]

An arterial branch from the aorta supplies each kidney. Small caliber collateral arteries enter the renal cortex through the fibrous capsule. [5] There is usually only one main artery, but roughly 5-10% of dogs have 2 main arteries. This variation is primarily noted in the left kidney. [5, 6] The main renal artery divides into 2 primary branches (dorsal and

ventral), which subdivide into 2 to 4 secondary interlobar arteries. [5] These interlobar arteries branch into arcuate arteries at the corticomedullary junction. Arcuate arteries divide into numerous interlobular arteries, which eventually branch into afferent arterioles. Afferent arterioles further divide into a dense capillary network to form glomeruli. [4] Glomerular capillaries merge to form efferent arterioles. Efferent arterioles lead to a second capillary network, the peritubular capillaries, that surround renal tubules. This arrangement forms a renal portal system between glomerular and peritubular capillaries linked by the efferent arteriole. This portal system is important in regulating hydrostatic pressures responsible for glomerular filtration. [4, 7, 8] By adjusting vascular resistance of afferent and efferent arterioles, kidneys can regulate hydrostatic pressures in glomerular or peritubular capillaries, thereby changing GFR and/or tubular reabsorption in response to homeostatic demands. [8] Peritubular capillaries eventually form venules, which join with interlobular veins. The renal venous system parallels the arterial system and terminates in the caudal vena cava. [3, 4]

***Renal Function***

Normal renal function relies on adequate perfusion of kidneys, sufficient functional renal tissue, and a patent urine outflow tract. Although the kidneys receive about 20-25% of cardiac output, distribution of blood flow within the renal parenchyma is not uniform. High renal blood flow applies principally to cortical regions. Intrarenal control of blood

flow keeps renal blood flow (RBF) and GFR constant over a range of about 70 mm – 180 mm Hg via autoregulation. Autoregulation is defined as the capacity of an organ to maintain relative constancy of blood flow as blood pressure is altered. Autoregulation of GFR is a consequence of factors that maintain constancy of RBF. Within the range of 70-180 mm Hg, a major increase in blood pressure causes only a slight increase in blood flow. The most variable determinants of GFR are the glomerular hydrostatic pressure and glomerular capillary colloid osmotic pressure. The major function of autoregulation in the kidney is to maintain a relatively constant GFR over this range of blood pressure to enable precise control of excretion of water and solutes. Renal blood flow and GFR decrease acutely at blood pressures below 80 mm Hg and it is believed they stop completely below 50 mm Hg. The primary functions of autoregulation in most tissues are delivery of oxygen and nutrients, and removal of waste products. In the kidney, normal blood flow is much higher than required for these functions. Rate of blood flow is an indication of renal processes involved in regulation of extracellular fluid rather than renal metabolic demands. In the kidney, the significant variable, therefore, is GFR, not RBF. [8, 9, 10, 11]

***Measurement of Renal Function***

Renal function can be measured by a variety of methods. Although BUN and SCr are perhaps the simplest methods, they do not become abnormally increased until there is

severe renal disease (>75% nonfunctional nephrons). In addition, BUN and SCr measurements can be affected by extrarenal factors. Urea is less accurate than creatinine because it is generated by the liver as a product of protein metabolism. Urea levels are affected by diet, hepatic insufficiency, gastrointestinal hemorrhage, and fluid therapy[12,13,14] Urea is also partially reabsorbed by renal tubules and therefore may not accurately reflect renal function since it is affected by renal blood flow and hydration status. Creatinine is an end product of muscle metabolism and is less dependent on extrarenal factors. Cachexia may result in a lower SCr, or a highly muscled working dog may have a slightly higher SCr, but these values should remain within normal range.[12] Although BUN and SCr are useful because of their simplicity, reproducibility, and low cost, they are only crude indicators of renal function.

Calculation of the clearance rate of a specific substance from is the most accurate method to quantitatively measure renal function.[11, 12, 15] Clearance is defined as the volume of plasma from which a specific substance is completely removed by the kidney per unit time and is used to calculate GFR.[12, 15] The ideal substance is one that is neither secreted nor reabsorbed by tubules, is freely filtered by glomeruli, is not metabolized or stored in the kidney, is minimally protein bound, and is nontoxic. Inulin and creatinine have been the most commonly used substances.[12, 16] Although clearance rates are accurate, they are technically difficult to perform since they require collection of multiple timed urine

samples, which may necessitate urinary catheterization or the use of a metabolic cage. Technical errors during urine collection and measurement may result in inaccurate GFR determination. Multiple blood samples are also required for these techniques.[15, 16] These methods are invasive and time-consuming, and clearance rates only provide information regarding total renal function. Another method of measuring renal function is to determine the plasma clearance rate of a compound after a single intravenous injection of a substance that is completely filtered by the glomerulus. Commercially available radiographic contrast media can be administered intravenously, and GFR can be determined by analysis of a plasma concentration versus time curve. This method correlates well with creatinine clearance but still only provides information regarding total renal function. [17]

Quantitation of individual kidney function by exogenous inulin or endogenous creatinine clearance requires invasive procedures to catheterize each ureter and introduces unnecessary risks and stress to the patient.[18] Quantitative renal scintigraphy provides a non-invasive, reliable method to measure both total and individual renal function.

A radiopharmaceutical is a chemical substance that contains a radionuclide, and radiopharmaceuticals can be formulated to deliver the radionuclide to a specific area of the body.[19] Technetium-99m is the most commonly used radionuclide and is one of the

most common radiopharmaceuticals used to measure GFR. It is excreted rapidly in the kidney by glomerular filtration with no tubular reabsorption or secretion and with insignificant protein binding. [20, 21, 22] Technetium-99m undergoes decay by transition to $^{99}$Tc as it releases gamma rays, which can be detected by a gamma camera to produce an image termed a scintigram.[18, 19]

The gamma camera consists of several components including a collimator, scintillation detector, pulse height analyzer, and recording device. [23] The scintillation detector incorporates a thin, wide thallium activated sodium iodide (NaI(TI)) crystal. When a gamma ray photon is absorbed by this crystal, a flash of light is produced. Light flashes are detected by a series of photomultiplier tubes, and information is used to generate electrical signals received by a pulse height analyzer. Detection of scatter radiation can be minimized by collimation and by setting the pulse height analyzer to accept only signals based on a unique amplitude signal for the specific radionuclide (i.e. $^{99m}$Tc). Signals accepted by the pulse height analyzer are counted by the recording device.[23] During acquisition of a scan, geometric distribution of counts is maintained to create a digital image composed of rows and columns of individual picture elements known as pixels.[24] Pixels are displayed on the computer screen monitor with the brightness of each pixel being proportional to the number of detected counts.[24] Thus the image represents both geometric distribution and activity. In renal scintigraphy, calculation of GFR from

the number of detected counts is derived from results of linear regression analysis of the percent total renal uptake of $^{99m}$Tc-labeled diethylenetriaminepentaacetic acid ($^{99m}$Tc-DTPA) against inulin and creatinine clearance rates.[25, 26] The general formula derived from these analyses is:

GFR (ml/min) = (% total renal uptake $^{99m}$Tc-DTPA) (regression coefficient) + (intercept)

Estimation of GFR based on quantitative renal scintigraphy is less consistent than plasma clearance studies in dogs with normal renal function. This is due in part to the short sampling period (approximately 2 minutes total). Autoregulatory mechanisms will alter GFR to accommodate changes in RBF and blood pressure, and thus GFR measurements may vary considerably in dogs with normal renal function or significant renal functional reserve capacity. Glomerular filtration rate values may be within normal limits but may vary on repeat scans due to normal homeostasis. [20, 21] Values for GFR are more consistent in dogs with renal insufficiency because kidneys are functioning at maximum capacity and have lost their precise autoregulatory ability. Considerations that may affect consistency of GFR measurements based on quantitative renal scintigraphy are motion artifact, gamma camera inaccuracies, placement of regions of interest, and calculation of depth correction factors.[20] Uptake of $^{99m}$Tc-DTPA in the dog depends on hydration status, cardiac function, and integrity of the renal vascular system. [27] The relatively short time required to collect images makes the technique easier to perform in veterinary

patients and can allow the procedure to be done without sedation. If sedation is needed to prevent motion artifact during the acquisition phase, studies have shown there is no significant effect of commonly used sedation protocols on GFR measurements. [28, 29] Studies have demonstrated that GFR estimation in dogs using $^{99m}$Tc-DTPA correlates well with both inulin and endogenous creatinine clearance rates.[15, 26] When regression coefficient and intercept based on inulin clearance is substituted, the equation becomes: GFR (ml/min) = (depth-corrected % renal uptake$^{99m}$Tc-DTPA) 0.194 + (-0.37). The regression coefficient and intercept using creatinine clearance has also been determined. Substitution of these values yields the following equation: GFR (ml/min) = (depth-corrected % renal uptake$^{99m}$Tc-DTPA) 0.171 + (-0.15). [15, 20] In dogs, the percentage dose of $^{99m}$Tc-DTPA that accumulates in the kidney during 1-3 minutes following injection yields the most accurate estimation of GFR. After 3 minutes, $^{99m}$Tc-DTPA flow into the collecting system decreases accuracy of GFR measurement. [26] Quantitative renal scintigraphy provides an immediate indication of renal function, is sensitive enough to detect changes in renal function before either BUN or SCr have changed, and provides GFR values for individual kidneys.

## Literature Review – Nephrotomy

The first formal investigation regarding functional impairment caused by nephrotomy was conducted by Moore and Corbett in 1911. Their results were not conclusive, but their observations and descriptions emphasized morphologic damage as a result of nephrotomy. They attributed much of the structural renal damage to methods used to achieve hemostasis rather than the actual incision. Their findings emphasized the following points: 1) renal surgery destroys renal tissue, 2) incision of the kidney causes less harm than methods used to provide hemostasis, 3) renal capsular closure alone is not sufficient to provide hemostasis, 4) mattress sutures placed transversely through the kidney destroys renal tissue, and 5) renal function is reduced following renal surgery.[30] Later studies conducted in animals were better controlled and specifically designed to assess renal function and characterize morphologic changes in kidneys following nephrotomy. A decrease in renal function was observed, but measurements used were not sensitive enough to accurately quantitate the decline in renal function. In 1923, Magoun reported azotemia based on elevated blood urea in 14 out of 23 animals following nephrotomy. In 1928, Deming demonstrated a 33% loss in renal function based on decreased phenolsulphonaphthalein (PSP) excretion following renal surgery.[2] Controversy regarding renal surgery and concern over potential risks associated with nephrotomy prompted further research evaluating effects of nephrotomy on renal function.

Maddern evaluated effects of nephrotomy in pigs because the porcine kidney morphologically resembles the human kidney. Bisection nephrotomies were performed in 24 animals separated into two groups of 12. A different method of nephrotomy closure was used in each group. Nephrotomies in the first group were closed using a simple continuous pattern to close both the renal pelvis and capsule. Individual arteries within the parenchyma were ligated if necessary. Four mattress sutures were placed through the parenchyma at the level of the corticomedullary junction and tied over pieces of muscle. Nephrotomies in the second group were closed in the same manner except no mattress sutures were used. Renal function was assessed via creatinine clearance at the time the animals were euthanatized. Results showed decreased renal function in all animals. Average residual renal function was 54% in the group with mattress sutures, and 64% in the group without mattress sutures.[2]

Gahring investigated effects of nephrotomy in dogs, comparing closure with and without sutures.[31] Twelve clinically normal dogs were divided into two groups. Renal function was assessed using a single injection of $^{131}$I-sodium iodohippurate to determine effective renal plasma flow and $^{125}$I-sodium iothalamate to determine GFR. Preoperative CBC, SCr, and UA were performed. A right nephrectomy was performed in all dogs, and excised kidneys were preserved for histologic evaluation. In several dogs renal function studies were repeated 4 weeks following nephrectomy. Left bisection nephrotomy

extending to the level of the renal pelvis was performed in all dogs that had undergone right nephrectomy. Renal vascular occlusion was accomplished with digital pressure; total renal ischemia was 10-15 minutes. Six nephrotomies were closed with horizontal mattress sutures placed through the parenchyma using 2-0 chromic gut followed by a simple continuous capsular closure with 4-0 chromic gut. Six nephrotomies were closed by applying digital compression to the bisected kidney segments. Renal function studies were performed in selected dogs at 2-3 days, 7-10 days, 3 weeks, and 6 weeks following nephrotomy. At 6 weeks, dogs were euthanatized and the left kidney was harvested for histologic comparison with the previously harvested right kidney. This study concluded that bisection nephrotomy reduced renal function by 20-40% compared to baseline.[31] The reduced renal function was reported to improve over a period of weeks. Gahring's results describing reduced renal function following nephrotomy are often referenced in veterinary textbooks.

Fitzpatrick further examined effects of nephrotomy on renal function in normal dogs. He used 16 dogs to compare 4 different nephrotomy techniques: extended sinus, radial paravascular, anatrophic intersegmental, and bisection.[32] Nephrotomies were performed on the left kidney in all dogs, and the right kidney served as a control. Dogs were re-anesthetized 48 hours following nephrotomy and both ureters were transected and catheterized. Renal function was evaluated by comparing creatinine, inulin, and p-

aminohippuric acid (PAH) clearance values between operated and control kidneys, and between groups. No preoperative renal function tests were performed to establish a baseline. Dogs were euthanatized at the end of the urine collection period and both kidneys were removed for histologic comparison. This study concluded that bisection nephrotomy reduced renal function by 50% in the operated (left) kidneys compared to the control (right) kidneys. Radial and anatrophic intersegmental nephrotomy techniques also reduced renal function in the operated kidney compared to the control kidney (20% and 30% respectively).[32]

Taguchi conducted a human clinical trial investigating bisection nephrotomy closed with a series of one-layer interrupted parenchymal sutures.[33] Incision length varied with size and location of the stone. Incisions were closed with 2-0 plain gut. The first bite of each suture engaged the capsule and entered the ipsilateral parenchyma to the level of the pelvis, where it engaged pelvic mucosa, then exited through the contralateral parenchyma and capsule to form a loop. Sutures were pre-placed at intervals of about 1.5 cm and were tied with enough tension to approximate incision edges. Average total renal ischemic time was 18 minutes 5 seconds. Renal function was assessed before and after surgery in 9 patients. Renal plasma flow decreased by 16% and GFR decreased by 20% initially, but these values returned to baseline within 2 weeks following surgery. Renal function based on BUN, SCr, creatinine clearance, and PSP remained normal 4 and 8

weeks following surgery. Blood urea nitrogen, SCr, and 24-hour creatinine clearance were evaluated 2, 4, and 8 weeks following surgery. Results of these measurements were within normal limits.[33]

Stone et al investigated effects of bisection versus intersegmental nephrotomy on renal function and morphology in normal dogs.[34] Fifteen healthy adult female dogs were divided into 5 groups of 3 dogs each. Dogs were determined to be healthy based on physical examination, BUN, SCr, and UA. Measurement of baseline GFR using $^{99m}$Tc-DTPA was determined in all dogs. Dogs were anesthetized and a ventral midline celiotomy was performed. An infusion of mannitol was given prior to renal arterial occlusion to attenuate the reduction in RBF. Indigo carmine was injected into a peripheral vein to aid in defining the intersegmental plane. An intersegmental nephrotomy was performed on the left kidney, and a midline bisection nephrotomy was performed on the right kidney. Incision length was 4 cm in all kidneys and extended through the parenchyma to the level of the renal pelvis. Interlobar, arcuate, or interlobular arteries encountered during bisection nephrotomy were ligated and transected. Renal arterial occlusion was 9-11 minutes. All nephrotomies were closed with 4-0 PDS in a simple continuous pattern including primarily capsule and minimal parenchyma. Each kidney was then secured to the body wall to prevent undue motion during postoperative scintigraphic studies. Renal function was assessed by measuring

SCr, BUN, and GFR using $^{99m}$Tc-DTPA on days 1, 4, 8, 15, and 29 following surgery. One group of dogs was euthanatized at each time period, and both kidneys were harvested for morphologic comparison. Results of renal function studies showed no significant difference between groups in SCr, BUN, or GFR at any time period, compared with baseline measurements. Morphologic evaluation demonstrated greater intrarenal hemorrhage, cortical infarction, and cortical inflammation in the bisection nephrotomy than intersegmental nephrotomy in the early phases of healing, but by 4 weeks there was essentially no histologic difference between kidneys.[34]

## Renal Effects of Nephrotomy

A variety of nephrotomy techniques have been described in an effort to limit renal injury. Various suture materials and patterns have been suggested to provide hemostasis while minimizing tissue trauma. Many early surgeons ligated individual arteries and veins encountered within the renal parenchyma. Most surgeons recommended a continuous capsular closure to approximate cut surfaces, and additional interrupted mattress sutures through the renal parenchyma to insure adequate hemostasis if necessary. These mattress sutures caused considerable tissue trauma, and thus surgeons tied sutures over pieces of fat or strips of ribbon gauze in an attempt to limit injury.[2]

Advances in technology have resulted in less invasive methods of treating renal calculi. Various drugs and dietary modifications may dissolve stones or prevent their formation.[35] Lithotripsy is currently used for select cases in humans and dogs to fragment stones and allow elimination without surgical intervention. Nephrotomy is still commonly used in veterinary surgery because availability of lithotripsy is limited. Nephrotomy is most commonly performed in dogs to remove nephroliths, but is also indicated to evaluate the renal parenchyma and pelvis for possible causes of hematuria and to collect samples for histologic examination.[36]

Nephrotomy may affect renal function in a number of ways. Direct trauma to tissues during surgery results in destruction of nephrons and transection of vessels and lymphatics. Sharp incision of the kidney results in less damage than blunt trauma or fracture, but injury results in acute inflammation with vasodilation, increased vascular permeability, and local tissue necrosis.[37, 38, 39]

The process of wound healing may affect renal function. Renal wounds follow the continuum of healing seen in all tissues: inflammation, repair, maturation. The period of inflammation is characterized by wound debridement, restoration of circulation, and fibroblast mobilization. Mild injury may cause only a transient inflammatory response, however, if trauma is extensive, the response may be severe and lead to further tissue destruction secondary to the release of enzymes such as collagenases and proteinases from lysed cells. Gentle tissue handling, meticulous hemostasis, aseptic technique, and proper suture technique are important to prevent excessive inflammation. As wound healing progresses, fibroblasts proliferate and produce collagen. The kidney is primarily a cellular organ, which has a good regenerative capacity, but there will be a degree of fibrosis and loss of normal structure following injury.[37, 38, 39]

Histologic studies of kidneys following nephrotomy have demonstrated marked intrarenal hemorrhage with cortical infarction and necrosis immediately following wounding.

Nephron and tubular damage are localized to areas adjacent to injury. With repair and maturation of damaged tissues, nephrons and tubules regenerate or have minimal residual damage, and wedge-shaped infarcts may be noted in the cortical region.[2, 34, 38, 39]

Ischemia and reduced blood flow to the kidney occur secondary to renal vasculature occlusion or hypovolemia and may reduce renal function.[2, 38, 39] Ischemia may lead to acute tubular necrosis. Deprived of oxygen and metabolite exchange, tubular epithelial cells undergo degenerative changes such as swelling, vacuolation, and necrosis. Affected tubules may fill with necrotic cellular debris and casts. Regenerating epithelium may be present in areas where the basement membrane is intact. The ultimate outcome of ischemia varies from loss of tubules with replacement fibrosis or return to normal function with compensatory function of unaffected nephrons. In one study, ischemia of 20 minutes was shown to cause swelling and degeneration of tubular epithelium. Debris was present in tubules, and functional studies demonstrated a decrease in creatinine clearance and PAH.[40]

Anesthetic protocols may also affect renal function following surgery.[41, 42, 43] Acute tubular necrosis may occur following an ischemic event or following periods of hypovolemia or hypotension during which the animal is not able to compensate for unexpected reduction in oxygen delivery resulting in the inability to maintain RBF.

Decreased RBF results in death and exfoliation of tubular cells into the lumen causing obstruction. Human studies have documented that about 5% of patients develop renal insufficiency following hospitalization.[43, 44] Fluid therapy and pharmacologic intervention may be employed to maintain renal blood flow and GFR during anesthesia and surgery to minimize reduction in renal function.[41, 45]

## Dopamine Receptors

Dopamine (3,4-dihydroxyphenylethylamine) is a catecholamine produced in the kidney that is structurally related to norepinephrine and epinephrine. Dopamine acts as an agonist at α and β adrenoceptors, as well as dopamine receptors. Dopamine receptors were first demonstrated in the central nervous system and were classified as D1 and D2. There are at least two subtypes of peripheral dopamine receptors: DA-1 found in vascular smooth muscle and DA-2 found in sympathetic nerve endings.[46, 47, 48] Differential receptor activation explains why distinct cardiovascular and renal responses can be obtained with various doses of dopamine.[49] Low doses stimulate DA-1 and DA-2 receptors to cause vasodilation and increased RBF, which results in diuresis. Medium doses stimulate β1 adrenoceptors, which increase cardiac output and decrease systemic vascular resistance. Cardiac effects of dopamine are due to direct stimulation of β1 adrenoceptors and release of norepinephrine from sympathetic storage sites. At higher doses, α adrenoceptors are recruited causing peripheral vasoconstriction which increases systemic blood pressure and vascular resistance thus decreasing RBF.[46, 49] The dose range is variable, and individual responses are unpredictable, necessitating careful monitoring and titration to achieve the desired response. Dopaminergic effects generally predominate, but at higher doses adrenoceptors are activated, which may result in effects such as tachyarrhythmias, hypotension, myocardial or splanchnic ischemia, systemic vasoconstriction, or reduced GFR.[50, 51, 52, 53]

Dopamine receptors vary in number, affinity, and distribution and may affect different biochemical and physiologic responses, even within a single organ such as the kidney.[52,54, 55] Dopamine-1 receptors have been localized to the renal blood vessels, proximal convoluted tubules, and cortical collecting ducts. Stimulation of renal DA-1 receptors results in vasodilation and decreased renal vascular resistance. Dopamine-2 receptors have been identified presynaptically on sympathetic nerve terminals in adventitia of the renal vasculature and glomeruli. The role of DA-2 receptors in control of renal function is unknown, but stimulation results in inhibition of norepinephrine release and subsequent hypotension and bradycardia. Renal vasoconstriction and decreased glomerular filtration have been associated with DA-2 activation.[55] Endogenous renal dopamine acts predominantly at renal tubular DA-1 receptors causing diuresis and natriuresis rather than vasodilation and increased RBF achieved with activation of renal vascular DA-1 receptors.[55, 56]

## Fenoldopam – Selective DA-1 Agonist

Selective dopaminergic agents have potential beneficial actions including increased RBF, increased GFR, decreased renal vascular resistance, increased sodium excretion, and increased urine output without the effects associated with nonselective dopaminergic stimulation (vasoconstriction, tachycardia, dysrhythmias). Fenoldopam mesylate (6-chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-[1H]-3-benzazepine-7,8 diol methanesulfonate) is a specific dopamine-1 (DA-1) receptor agonist based on the 3,4-dihydroxyphenethylamine structure of dopamine that selectively stimulates DA-1 receptors to increase renal blood flow and improve renal function. Fenoldopam has been shown to be a potent renal vasodilator in several species including humans, monkeys, dogs, and rats resulting in increased RBF, decreased renal vascular resistance, increased GFR, and increased sodium excretion.[57, 58] Selective effects of fenoldopam are consistent over a wide dosage range with no significant effect on heart rate, even at extremely high doses.[59, 60] Vascular activity of fenoldopam appears to be restricted to postsynaptic DA-1 receptors, unlike dopamine, which appears to produce renal vasodilation by inhibition of vasoconstrictor tone through interaction with presynaptic DA-1 receptors.[59] Fenoldopam produces renal effects at low doses (0.03 μg/kg/min) and is effective as an antihypertensive agent as well as positively affecting renal function at higher doses (0.1-0.3 μg/kg/min) without cardiovascular changes in either hypertensive or normotensive patients.[45]

Fenoldopam reaches steady state concentration in about 20 minutes when administered as a constant infusion.[45, 61] Intravenous administration of fenoldopam acts selectively on DA-1 receptors in vascular smooth muscle to produce renal, mesenteric, cerebral, and coronary vasodilation.[59, 62] Previous studies in dogs have shown that fenoldopam preserves renal blood flow during hypovolemia and hypotension and prevents decreased GFR associated with acute nephrotoxicity.[63, 64, 65] Renal vasodilator effects have been demonstrated in both conscious and anesthetized normal dogs.[62, 66] Fenoldopam has been shown to maintain RBF and GFR in studies of human subjects with and without renal insufficiency.[50, 67, 68]

## Literature Review - Fenoldopam

Nichols investigated effects of fenoldopam in dogs with amphotericin B-induced nephrotoxicity.[65] Amphotericin B is an antimycotic antibiotic derived from *Streptomyces nodosus*. The drug interacts with sterols in cell membranes to change permeability and cause cell death. Although it is effective for treatment of fungal infections, it induces nephrotoxicity in about 80% of treated patients. Therapy may be discontinued in clinical patients if the decrease in renal function is substantial. Previous studies in humans and dogs evaluating nephrotoxic effects of amphotericin B showed decreased RBF and GFR during therapy. Nichols found that fenoldopam was renoprotective in dogs administered amphotericin B every other day for 8 days. Fenoldopam attenuated reduction of GFR and reversed initial reduction in sodium excretion and urine output caused by amphotericin B.[65]

Aronson et al demonstrated that fenoldopam preserved RBF even during fenoldopam-induced hypotension.[64] Ten adult male dogs were anesthetized and baseline measurements for RBF, heart rate (HR), blood pressure (BP), cardiac output, and pulmonary wedge pressure were obtained. An infusion of either fenoldopam or sodium nitroprusside (SNP) was administered to decrease mean arterial pressure (MAP) by 30% of baseline. Infusion continued for 15 minutes, and measurements were recorded. Infusion was discontinued and baseline variables were allowed to stabilize for 30

minutes. Next, the other drug (either fenoldopam or SNP) was administered, and measurements were recorded as previously described. The sequence was repeated for a total of four infusions. Mean fenoldopam dose required to achieve hypotension was 3.4 $\pm$ 2.0 μg/kg/min. Renal blood flow was preserved with fenoldopam but decreased with SNP. Heart rate and cardiac output measurements were not significantly different from baseline.[64]

Halpenny et al investigated effects of fenoldopam in normal dogs subjected to acute hypovolemia.[63] Eight female beagles were anesthetized and partially exsanguinated via controlled phlebotomy until RBF decreased to 60% of baseline. Fenoldopam administration resulted in increased RBF and increased creatinine clearance rates during hypovolemia.[63]

Lass and Ackerman worked independently to evaluate effects of fenoldopam in normal dogs.[62, 66] Lass focused on effects in anesthetized dogs. Baseline values were recorded for RBF, MAP, HR, and renal vascular resistance (RVR). Dogs were anesthetized and administered fenoldopam at either 0.1 μg/kg/min or 0.2 μg/kg/min. Fenoldopam increased RBF and decreased RVR at both infusion rates. There was a slight, but not significant, decrease in MAP at 0.2 μg/kg/min, however, HR did not change. Results showed that it is possible to produce selective renal vasodilation in anesthetized dogs

with fenoldopam.[62] Ackerman performed experiments in both conscious and anesthetized dogs. Results showed increased RBF and decreased MAP and RVR with intravenous administration of fenoldopam in anesthetized dogs. In conscious dogs, a similar increase in RBF and decrease in RVR was seen, but the decrease in MAP was not observed.[66]

Similar effects of fenoldopam were demonstrated in human studies. Murphy et al demonstrated that fenoldopam was effective in lowering BP with only a slight increase in HR in hypertensive patients.[68] Control hypertensive patients did not have a decrease in BP. Fenoldopam also increased RBF, GFR, and urine output, and decreased RVR. Glomerular filtration rate increased about 6% in hypertensive patients given fenoldopam compared to a similar decrease in GFR in control patients.[68] Schusterman compared effects of fenoldopam with nitroprusside in hypertensive patients with and without renal impairment. Fenoldopam caused an increase in GFR, urine output, and fractional excretion of sodium compared to nitroprusside in both groups.[67] Mathur evaluated effects of fenoldopam in normotensive healthy males.[50] Fenoldopam increased RBF and urine flow rates in patients given fenoldopam compared to patients given placebo. There was no change in HR or BP. In studies in hypertensive patients, fenoldopam increased both GFR and RBF suggesting a greater vasodilatory effect on renal arterioles in patients with pre-existing increased vascular tone.[50]

## Purpose of Study/Hypotheses

The purpose of this study was to evaluate effects of fenoldopam on renal function in normal dogs subjected to nephrotomy. In addition, effects of bisection nephrotomy on renal function in normal dogs were evaluated. We hypothesized that intravenous infusion of fenoldopam would maintain baseline renal function in normal dogs subjected to nephrotomy compared with baseline renal function in control dogs subjected to nephrotomy given intravenous infusion of physiologic saline. We also hypothesized that intravenous infusion of fenoldopam would result in maintenance of baseline renal function in the operated kidney compared with baseline renal function in the control kidney of normal dogs.

## Materials and Methods

***General Information**:*

Sixteen adult dogs (12 male; 4 female) were screened for normal general health based on results of physical and rectal examination, CBC, serum chemistry profile, urinalysis, and urine culture. Dogs were paired for approximate body weight, age, and sex. Each dog was randomly assigned to one of two groups: fenoldopam (F) or placebo (P). Investigators (DRW/NZP/DLB) and operating room assistants were blinded to treatment groups. Each pair of dogs was handled as a block throughout the experiment to eliminate potential variables that could introduce bias. All investigative methods were approved by the Animal Care and Use Committee of Virginia Polytechnic Institute and State University.

Dogs were housed in individual runs and allowed to acclimate to their environment for a minimum of 3 days prior to establishing baseline GFRs. Following acclimation, baseline glomerular filtration rate ($GFR_0$) was determined by renal scintigraphy using the method established prior to the onset of the experiment and described under *Renal Scintigraphy Protocol*. Surgery was performed on a single pair of dogs each day, and the surgery order, based on treatment group, was randomly assigned. Each surgeon (DRW/NZP) performed surgery on 4 dog pairs. Anesthesia and surgical technique were identical for all dogs as described under *Nephrotomy Protocol*.

Renal function was assessed by measuring BUN, SCr, and GFR on days 1, 21, and 42 after surgery. Blood was collected for measurement of BUN and SCr, and urine was submitted for analysis and culture prior to renal scintigraphy. Urinary tract infection was considered present if there was bacterial growth in urine samples collected by cystocentesis or sterile catheterization at scheduled evaluations. Dogs with positive urine cultures were given a course of amoxicillin (22 mg/kg PO TID x 7 days). Recheck urine cultures submitted at the next scheduled follow-up evaluation confirmed resolution of urinary tract infection in affected dogs. Postoperative scintigraphic protocol was identical to the preoperative protocol. All dogs were housed at the research facility a minimum of 6 weeks following surgery.

***Renal Scintigraphy Protocol**:*

The scintillation gamma camera was peaked daily to match the energy window of $^{99}$Tc. Quality control was performed daily to insure image uniformity in response to a uniform field of radiation. The camera was equipped with a low energy, general purpose, parallel-hole collimator, and a 2miC dose of $^{99m}$Tc-DTPA was used at a fixed distance to calibrate camera sensitivity.

Each dog was fasted for 12-24 hours prior to renal scintigraphy, and water was available. Each animal was sedated with intramuscular administration of medetomidine (11 μg/kg), butorphanol (0.22 mg/kg), and atropine (0.044 mg/kg).[29] A 20 gauge intravenous cephalic catheter was placed. Each dog was positioned on the scanning table in left lateral recumbency and gently restrained by two assistants. The camera was positioned against the spine for dorsal views. A 10 miC dose of $^{99m}$Tc-DTPA was housed in a lead-shielded syringe attached to the cephalic catheter by extension tubing loaded with heparinized saline. The extension tubing was then loaded with the entire dose of $^{99m}$Tc-DTPA and delivered as a bolus by a flush of 2 ml of heparinized saline. As radioactivity was observed uniformly in the lungs, a dynamic acquisition was initiated, collecting images for a total of 6 minutes. A right lateral view was obtained by rotating the camera $90^0$ into a position over the right mid-cranial abdomen without changing the dog's position. This image was used to measure renal depth and allow for incorporation of depth correction into activity measurements.[15]

Once imaging was completed, the intravenous catheter, empty dose syringe, flush syringe, and extension tubing were placed in a container to collect postinjection counts. This count represented the amount of $^{99m}$Tc-DTPA in the calculated dose that was not injected and therefore not available for renal filtration. Dogs recovered in the nuclear

medicine ward until radioactivity decreased to acceptable levels, and then animals were returned to their original runs (approximately 24-48 hours following scintigraphy).

Computer analysis of the scintigram was performed using a modified spreadsheet analysis (See Acknowledgement - *G. Daniel*). Initial acquisition consisted of 96 frames collected over 6 minutes. The first 48 frames (each of 0.75 seconds) represented the renal perfusion phase of the study (not reported here), and were collapsed into 6 frames of 6 seconds each. These were added to the second set of 48 images (each of 6 seconds) to represent the entire renal phase. This dynamic imaging sequence was used to calculate GFR. The resultant 54 images were summed to a single image from which regions of interest (ROI) were hand drawn around each kidney and cranial and caudal to each pole of each kidney for determination of background radioactivity.[21] The same radiologist (DLB) drew ROI and evaluated all scintigrams.[20, 25, 26]

***Nephrotomy Protocol:***

All dogs were fasted for 24 hours prior to surgery with water available free choice. Dogs were premedicated with morphine (0.25 mg/kg SQ) and anesthesia was induced with propofol (6 mg/kg IV to effect). Each dog was intubated and maintained at a surgical plane of anesthesia using isoflurane and oxygen. Lactated Ringer's solution was administered (22 ml/kg/hr) to all dogs through a cephalic catheter throughout anesthesia.

A second cephalic catheter was placed for administration of either fenoldopam or 0.9% saline. An arterial line was placed in the dorsal pedal artery to allow direct measurement of blood pressure.

Dogs were prepared for a standard ventral midline celiotomy. The surgical site was scrubbed with chlorhexidine and alcohol. A Foley catheter was placed in the urinary bladder, which was emptied before transporting dogs to the operating suite. Dogs were positioned in dorsal recumbency and the vital signs monitor (Protocol Systems; Model ProPaq 106) was connected. Baseline body temperature (T), HR, and respiratory rate (RR) measurements were recorded. The manometer was zeroed and baseline BP was recorded. After baseline measurements were recorded, a constant rate infusion (CRI) of either fenoldopam (Corlopam®; Abbott Laboratories, North Chicago, Ill) or 0.9% saline was started ($I_0$). Dogs in Group F received fenoldopam (0.1 µg/kg/min) and dogs in Group P received 0.9% saline (equivalent volume/kg/min). A mechanical programmable pump (Baxter; Model AS50) was used to ensure accurate delivery of the infusion over 90 minutes. Body temperature, HR, RR, and BP were recorded every 15 minutes during the CRI.

A standard ventral midline celiotomy was performed and the left kidney was exteriorized. The renal artery was isolated, and a bulldog clamp was placed a minimum of 20 minutes

after $I_0$ **(Figures 1 & 2)**. Renal arterial occlusion was maintained for 15 minutes in all dogs.[40] The convex surface of the kidney was measured with a sterile ruler **(Figure 3)**. The nephrotomy incision length was standardized to 2/3 the length of the kidney and the renal capsule was marked with electrocautery.[36] Once the artery was occluded and the kidney blanched, nephrotomy was performed along the premeasured site and continued to the level of the renal pelvis using both sharp and blunt dissection. The renal pelvis and proximal ureter were catheterized using a 3.5 French red rubber catheter **(Figure 4)**. The nephrotomy incision was closed with 4-0 PDS in a simple continuous pattern taking care to include primarily capsule and only rarely minimal renal parenchyma **(Figure 5)**. The bulldog clamp was removed after exactly 15 minutes of arterial occlusion. The incision was inspected for hemorrhage and hemostasis assured as renal perfusion was re-established **(Figure 6)**. The abdomen was closed routinely. Administration of the CRI continued for exactly 90 minutes in all dogs. Anesthesia was maintained until the CRI was stopped ($I_{90}$). Body temperature, HR, RR, BP measurements and urine volume were recorded immediately at $I_{90}$. Intravenous and arterial catheters were removed, and the dog was moved to a recovery cage. The urinary catheter was left in place until the following day to allow urine quantitation and facilitate sample collection. Morphine (0.25 mg/kg SQ) was given during the first 24 hours to provide postoperative analgesia.

### *Statistical Analysis*

Data were analyzed using SAS software. Paired t-tests were used to compare values for T, HR, RR, BUN or SCr, and GFR between the two groups prior to beginning the project. Multivariate repeated measures analysis was used to examine treatment and time effects on each variable. Multivariate repeated measures analysis was used to examine effect of time, treatment, and surgeon on BUN, SCr, and GFR. A t-test was performed to determine if there was an effect of surgery on either total or individual GFR at each time period. Significance was determined at $p < 0.05$.

## Results

There were no complications associated with surgery or scintigraphy in any dog. One dog had moderate hemorrhage from the nephrotomy incision when renal blood flow was reestablished, and a single horizontal mattress suture was placed superficially in the renal parenchyma to achieve hemostasis. All nephrotomy closures were completed prior to release of the bulldog clamp. All abdominal closures were completed prior to the end of the CRI. Several dogs had gross hematuria for 1 to 3 days following surgery, which resolved without therapy. Urinary tract infections were diagnosed in the postoperative period in 50% of the dogs during the course of the study, and all resolved following short-term antibiotic therapy. There was no significant difference in incidence of urinary tract infections between groups.

There was no significant difference in baseline values (T, HR, RR, BUN, SCr, GFR) between groups prior to beginning the study. Perioperative measurements of T and RR were not significantly different between groups. Blood pressure measurements remained within established normal ranges in both groups while dogs were under anesthesia **(Graph 1).** Perioperative heart rate was not significantly different between groups **(Graph 2).** Urine output was normal in all dogs in both groups.

No difference associated with treatment group or surgeon was found for either BUN or SCr. Blood urea nitrogen and SCr varied individually in animals of both groups but generally stayed within normal ranges (BUN: 8-28 mg/dL, SCr: 0.5-1.3 mg/dL). Blood urea nitrogen increased above the reference range (52 mg/dL) for one out of 64 measurements in Group P (mean BUN: F=12; P=15), and SCr was increased (1.6 mg/dL and 1.9 mg/dL) for 2 out of 64 measurements in Group P (mean SCr: F=0.9; P=1.06). These variations were not statistically significant and did not correlate with decreased GFR **(Graphs 3 & 4)**. In addition, there was no difference in either total or individual GFR associated with treatment, surgeon, or time **(Graphs 5 & 6).** Further, there was no statistically significant difference in GFR values between operated and control kidneys **(Graph 7).**

## Discussion

As discussed earlier, nephrotomy may affect renal function in a number of ways. Direct trauma to tissues during surgery may result in destruction of nephrons and transection of vessels and lymphatics. The process of wound healing results in inflammation, edema, and eventually fibrosis. Ischemia and reduced blood flow to the kidney may cause a reduction in renal function secondary to acute tubular necrosis.[2, 38, 39] In addition, anesthetic techniques may affect renal function following surgery.[41, 44, 43] Pharmacological intervention may be used to maintain renal blood flow and GFR during anesthesia and surgery to minimize reduction in renal function.[45] Previous studies reported a decline in renal function of 20-50% following nephrotomy in normal dogs.[31,32] Our study cannot be directly compared to earlier studies due to differences in anesthetic protocol, surgical technique, and renal function measurement.

In the study described by Gahring, anesthesia was induced with thiamylal sodium, dogs were intubated, and a surgical plane of anesthesia was maintained with methoxyflurane.[31] Fitzpatrick et al induced and maintained a surgical plane of anesthesia with sodium pentothal.[32] Barbiturates do not directly affect kidneys, but they may affect renal function secondarily by decreasing cardiovascular function.[41, 42] Methoxyflurane has been associated with acute renal failure in humans following anesthesia. Effects of methoxyflurane on the renal system in dogs are unknown, but it can cause mild to

moderate hypotension and decreased cardiac output.[41, 42] In the current study, propofol was used to induce anesthesia, dogs were intubated, and a surgical plane of anesthesia was maintained with isoflurane. Propofol is a rapid-acting, ultra short, non-barbiturate drug that produces dose-dependent decrease in arterial blood pressure but has no direct effects on renal function.[41, 42] Isoflurane may decrease cardiac contractility, but cardiac output is maintained, and there is no reported change in renal function in dogs.[41, 42]

Administration of intravenous fluids during anesthesia assists in maintaining effective circulating blood volume and cardiac output. Most drugs used for anesthesia decrease cardiac output and arterial blood pressure to some degree. In dogs, a fluid infusion rate of 10-22 ml/kg/hr is suggested to maintain normal cardiovascular function.[41] Previous nephrotomy studies did not describe the use of adequate volumes of intravenous fluids during anesthesia, nor was blood pressure measured during anesthesia.[31, 32] In the current study, intravenous fluids were administered at 22 ml/kg/hr in all dogs from the time of anesthetic induction until anesthetic recovery. Sufficient blood loss during surgery without concurrent administration of intravenous fluids could decrease cardiac output and renal blood flow, which may adversely affect renal function.[43, 44]

Differences in surgical technique could also explain the decrease in renal function reported in earlier studies. It has been suggested that the injury caused by incising the

kidney is less than that caused during closure of the wound.[2, 38] Mattress sutures placed through renal parenchyma cause ischemic tissue damage and renal necrosis leading to eventual fibrosis.[2] Gahring used horizontal mattress sutures in one group of dogs; Fitzpatrick used vertical mattress sutures to close the bisection nephrotomies.[31, 32] In the current study, nephrotomies were closed with a simple continuous capsular suture pattern. Renal arterial occlusion time has also been shown to affect renal function. In a study evaluating change in renal function following complete ischemia of the kidney in dogs, renal arterial occlusion of more than 20 minutes was associated with marked reduction in renal function.[40] Renal arterial occlusion time was not standardized in Gahring's work, however, a mean renal ischemic time of 10-15 minutes was described.[31] Fitzpatrick et al standardized renal arterial occlusion to 30 minutes in dogs undergoing bisection nephrotomy.[32] In the current study, renal arterial occlusion was 15 minutes in all dogs.

Renal function can be measured by a variety of methods. In the current study, renal function was evaluated by BUN, SCr, and quantitative renal scintigraphy. Blood urea nitrogen and SCr are regarded as insensitive indicators for change in renal function and only become increased when > 75% of nephrons are nonfunctional.[13] Quantitative renal scintigraphy is a more sensitive measure of renal function than BUN or SCr. It provides a quick, non-invasive, reliable measurement of both total and single kidney GFR,

identification of subclinical renal disease prior to increase of BUN or SCR, and quantitation of disease severity.[20] The $^{99m}$Tc-DTPA used in the current study is a common radiopharmaceutical used to measure GFR. It accumulates rapidly in the kidney via glomerular filtration with no tubular reabsorption or secretion.[20] Previous studies have demonstrated that GFR estimations using $^{99m}$Tc-DTPA correlate well with inulin and endogenous creatinine clearance rates.[26, 27] Total GFR values above 3 ml/min/kg are considered normal in the dog. Dogs with subclinical renal insufficiency have total GFR values between 1.2 and 2.5 ml/kg/min, and values below 1.0-1.3 ml/kg/min are often associated with an increase in BUN and SCr.[20] One dog in this study had total GFR in the subclinical range at one time period, but all other GFR measurements for this dog were within normal range. Dogs with normal renal function or subclinical renal insufficiency have adequate functional renal reserve that allows for adjustment of GFR by renal autoregulation to maintain homeostasis, therefore, GFR values may fluctuate on repeat scans.[8, 10, 20] Normal BUN and SCr values imply that dogs in this study had adequate renal functional reserve to prevent azotemia following nephrotomy. Dogs who have lost functional reserve are operating at maximal GFR, and therefore repeat scans vary less, and calculated GFR values more closely estimate true renal function.[20] Results of this study showed total GFR did not change following nephrotomy in normal dogs, and fenoldopam did not affect GFR in these dogs.

Our findings in this study were unexpected since nephrotomy was previously reported to cause a 20-50% decrease in renal function in normal dogs.[31, 32] Even if adequate functional renal reserve remained following nephrotomy to prevent an increase in BUN or SCr, or a decline in total GFR, the acute trauma associated with surgery should have produced a decline in individual GFR of the operated kidney.[2]

An advantage of renal scintigraphy is that it enables measurement of individual GFR. There are no defined normal limits for individual kidney GFR, but logic would suggest each kidney contributes roughly 50% to total GFR. In the current study, mean individual GFR for the operated kidney was 45.2% (range: 31.5% – 67.4%). Statistical analysis showed no difference in individual GFR between treatment groups. There was also no significant difference in GFR between operated and control kidneys, and this suggests bisection nephrotomy does not reduce GFR in normal dogs.

Fenoldopam mesylate is a selective DA-1 receptor agonist that has been shown to act as a rapid vasodilator in a variety of species, including humans, monkeys, rats, and dogs, resulting in increased RBF, decreased renal vascular resistance, and increased GFR.[57, 58] The selective effects of fenoldopam are consistent over a wide dosage range without significant effects on heart rate even at extremely large doses.[59, 60] It is about 6-10 times

more potent than dopamine as a DA-1 agonist.[54, 62] It has no significant affinity for DA-2 receptors, $\alpha_1$ or $\beta$ adrenoceptors at therapeutic doses and thus does not produce adverse cardiovascular effects observed with nonselective dopamine agonists.[57, 62] Plasma half-life of fenoldopam is about 4-5 minutes and does not change with dose; steady state plasma levels are achieved within 20 minutes.[45, 61] Previous studies demonstrated a renoprotective effect in dogs in situations of acute hypovolemia, hypotension, and nephrotoxic acute renal failure.[63, 64, 65] Fenoldopam doses used in these earlier studies were similar to the dose used in the current study. Based on these studies, fenoldopam appears to maintain RBF and GFR when renal function is compromised.

Our model to reduce renal function via bisection nephrotomy was not effective for our purpose in this study. We based our study on the assumption that nephrotomy would decrease renal function by 20-50%, which should have been sufficient to evaluate the renoprotective effects of fenoldopam. There was no significant difference in GFR between control and operated kidneys compared with baseline measurements at any time point following nephrotomy. There was no significant difference in renal function as measured by BUN, SCr, or GFR between groups at any time. Since nephrotomy did not reduce renal function in this study, we cannot say if fenoldopam had a renoprotective effect during nephrotomy in normal dogs. Further research evaluating this drug is

warranted. It may be beneficial to investigate perioperative effects of fenoldopam in dogs with pre-existing renal insufficiency.

## Conclusion

In summary, our results neither support nor refute the potential perioperative renoprotective effects of fenoldopam in normal dogs, since bisection nephrotomy did not induce a significant reduction in renal function. We conclude that bisection nephrotomy, as described in our study does not cause a significant decrease in renal function. This conclusion supports a recently reported finding by Stone et al.[34] While nephrotomy, as described in earlier studies, reduced renal function, bisection nephrotomy using a simple continuous capsular closure and renal arterial occlusion of less than 20 minutes, had no adverse effect on GFR as measured by quantitative renal scintigraphy using $^{99m}$Tc-DTPA.[31, 32]

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## Appendix A

**Figure 1**

Left Kidney: Renal artery isolated (*white arrow*) from renal vein (*arrow head*).

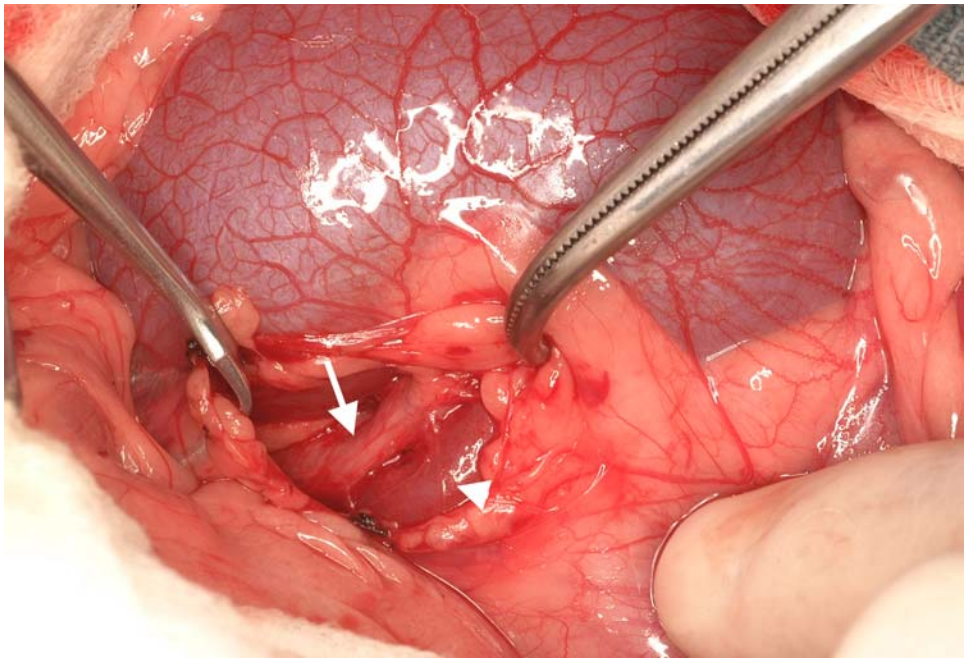


**Figure 2**

Left kidney: Isolated renal artery occluded with bulldog clamp (*arrow).*

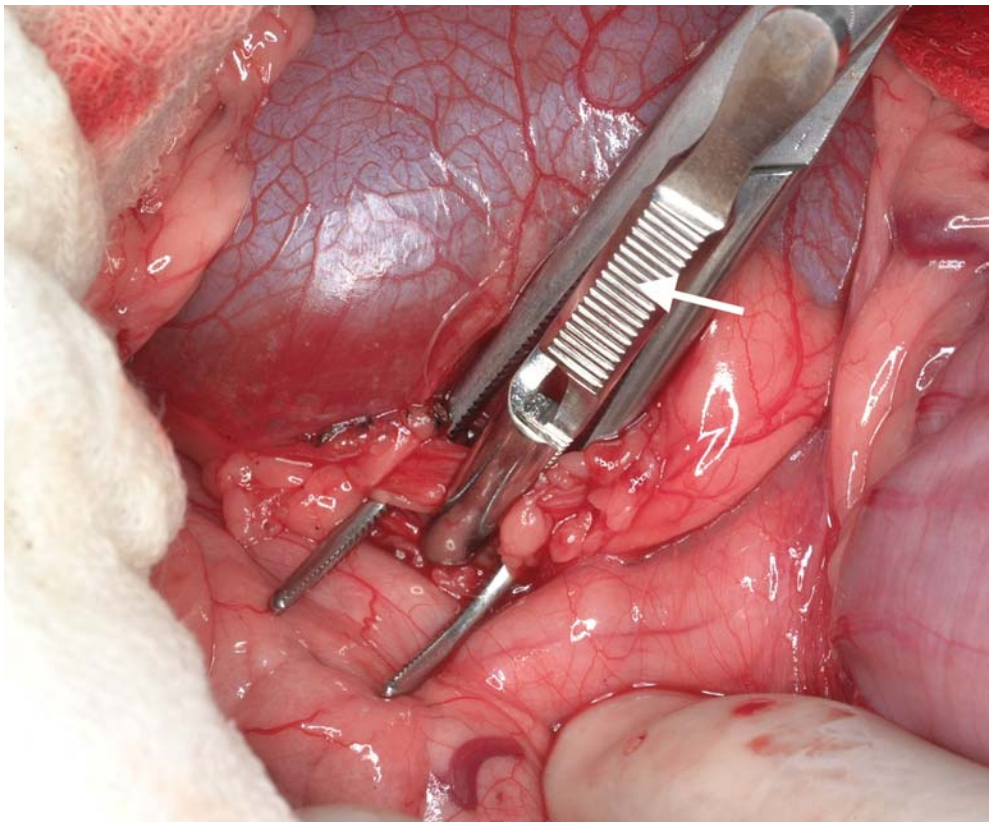


**Figure 3**

Left Kidney: Nephrotomy length standardized to 2/3 the length of convex surface of kidney as measured with a sterile ruler.

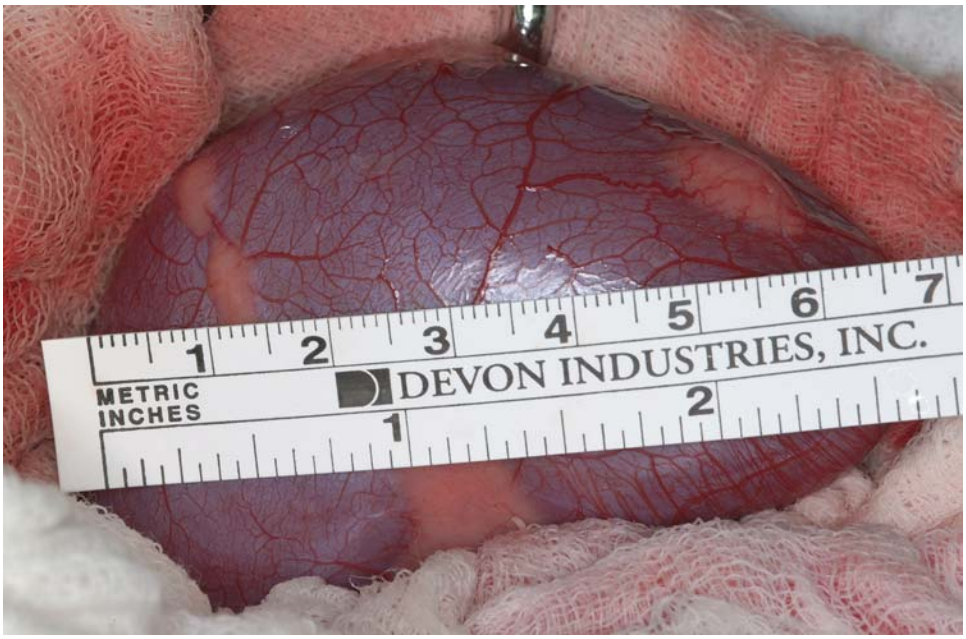


**Figure 4**

Left Kidney: Nephrotomy extends 2/3 length of convex surface (marked with electrocautery – *white arrows*); 3.5 French red rubber catheter (*black arrow*) introduced through nephrotomy and passed into renal pelvis and proximal ureter.

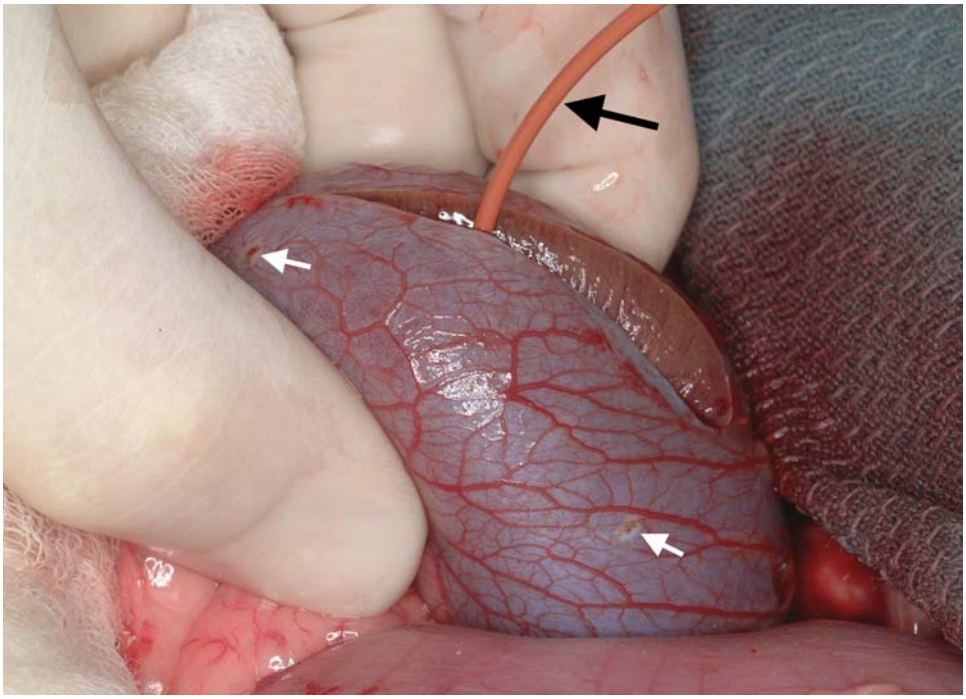


**Figure 5**

Left Kidney: Closure of nephrotomy performed using 4-0 PDS; closure included renal capsule and minimal renal parenchyma.

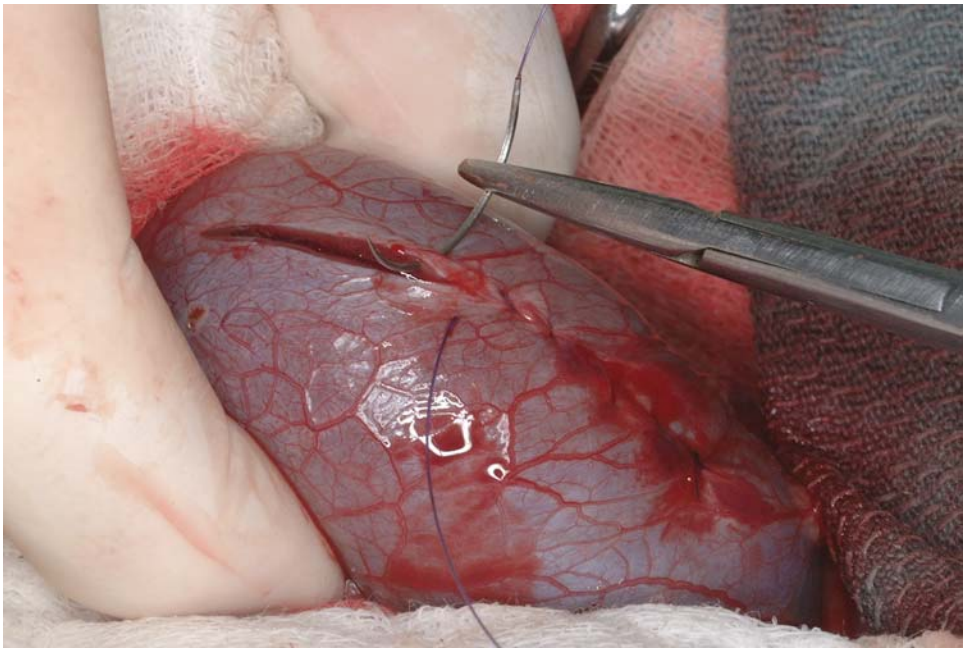
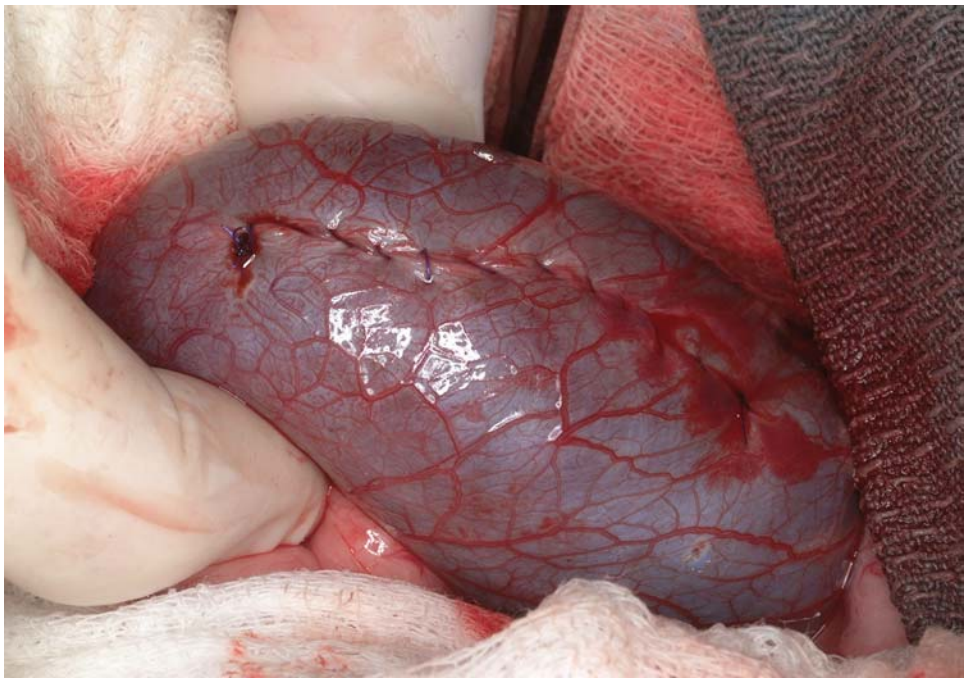


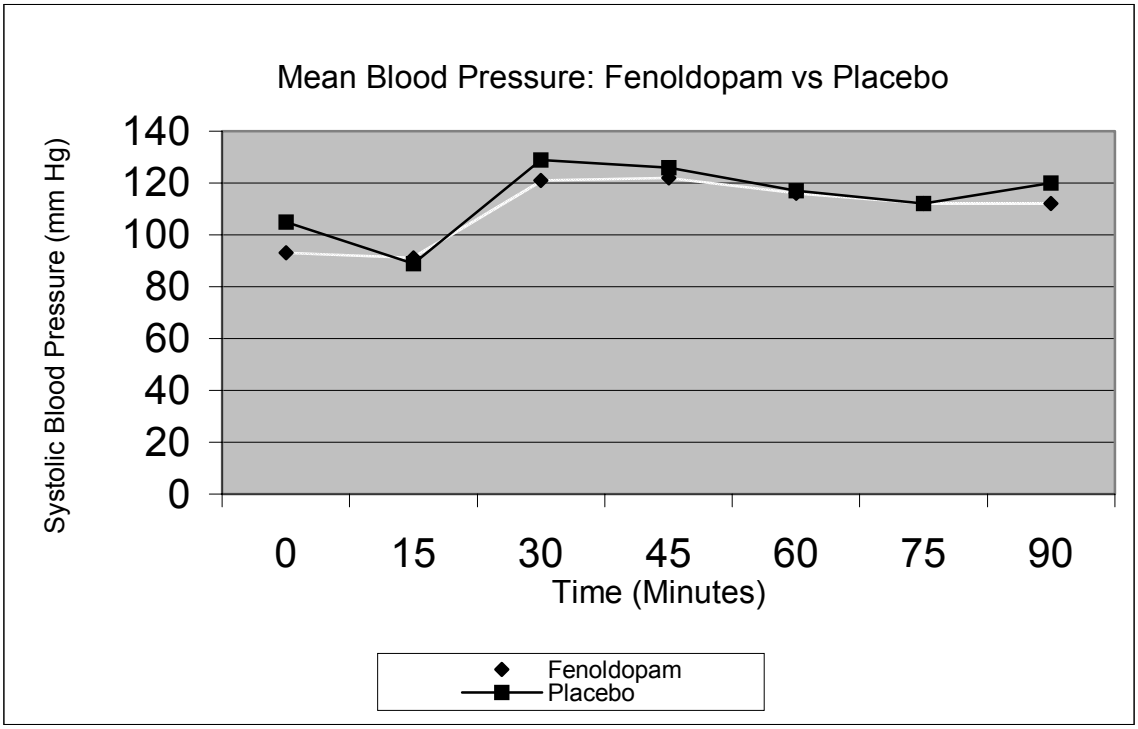
**Figure 6**

Left Kidney: After closure, bulldog clamp was removed and incision inspected for active hemorrhage.

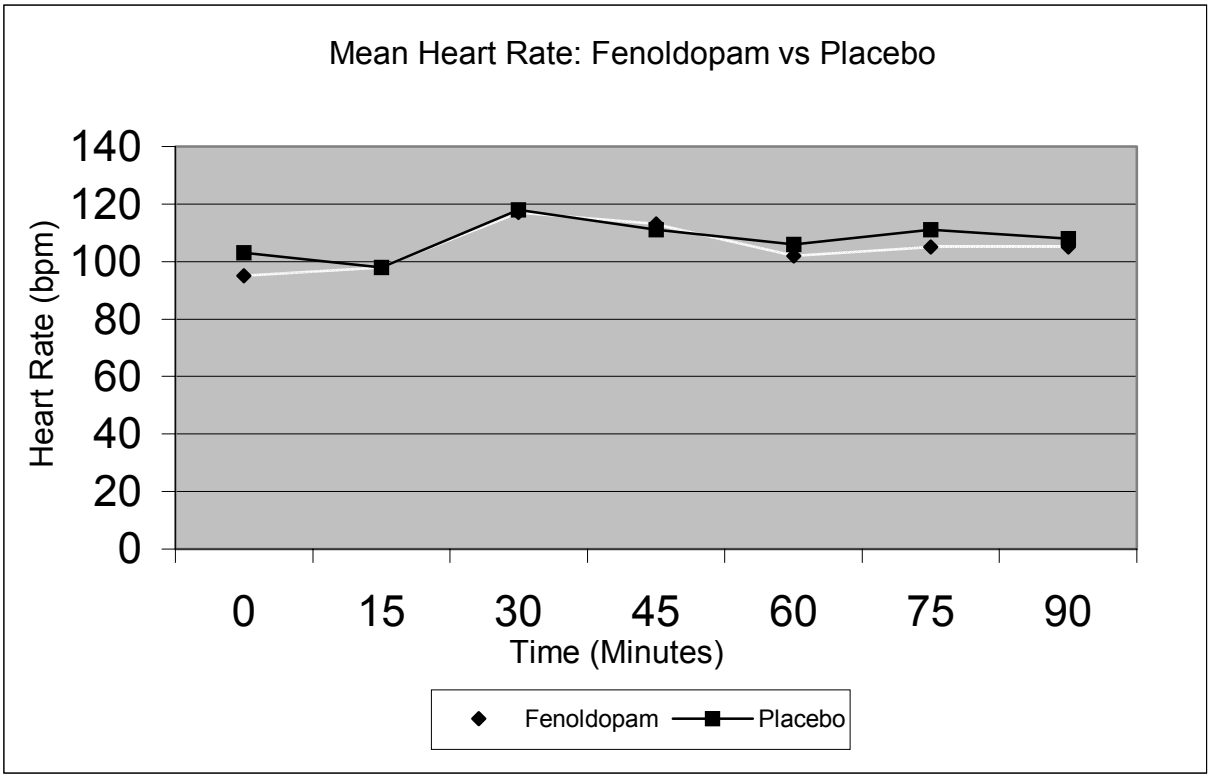


## Appendix B

**Graph 1**



**Graph 2**

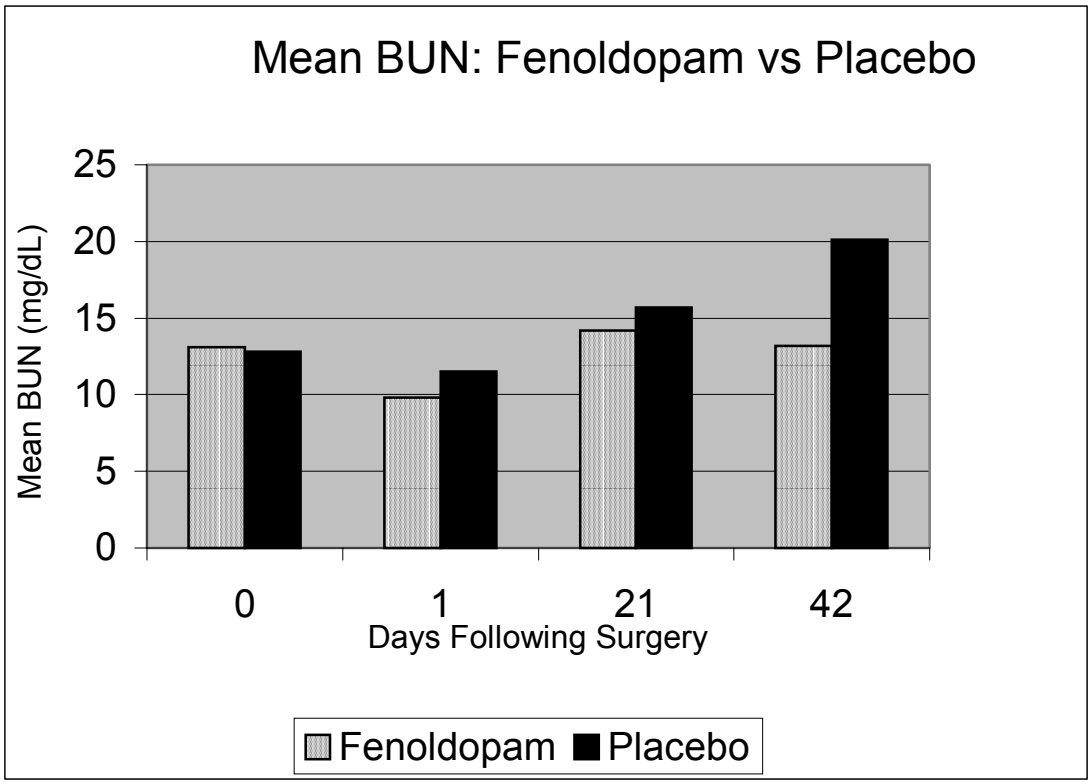

Mean Heart Rate: Fenoldopam vs Placebo
Heart Rate (bpm)
140
120
100
80
60
40
20
0
0
15
30
45
60
75
90
Time (Minutes)
Fenoldopam
Placebo

**Fenoldopam Dilution:**
Add one ampule (10mg/ml) of fenoldopam to 50 ml of 0.9% Saline = 200 μg/ml
Deliver as constant rate infusion at 0.1 μg/kg/min

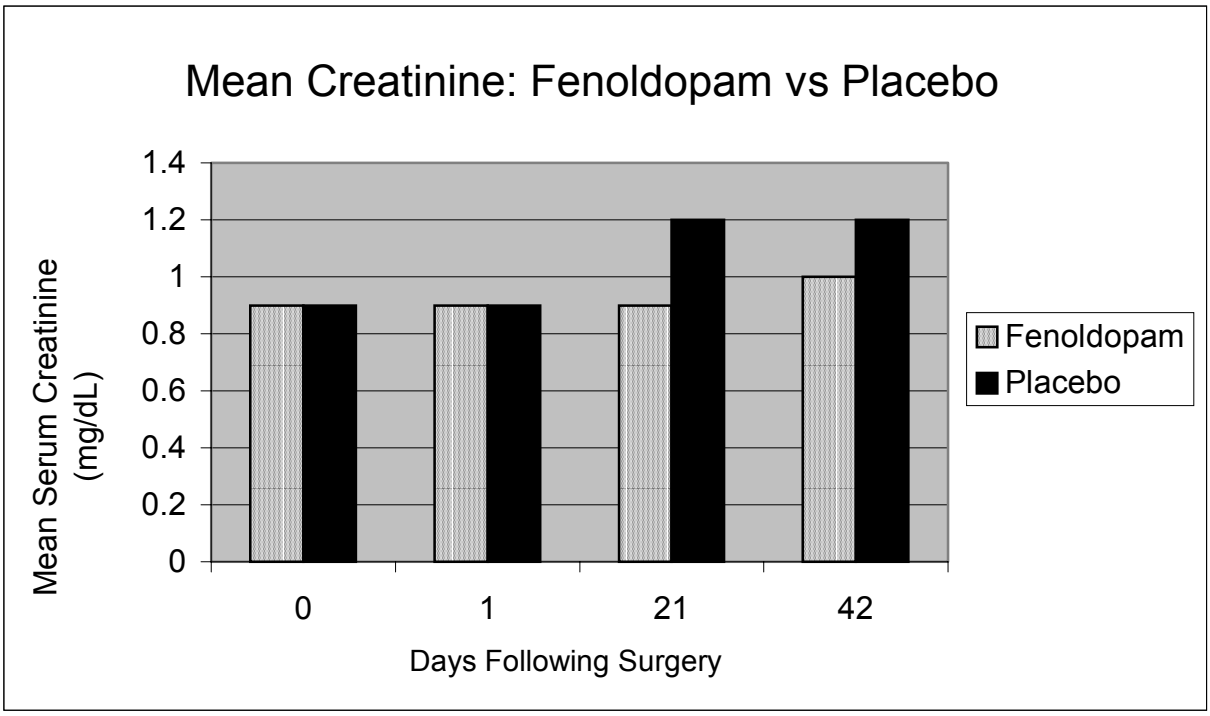
## Serum Creatinine and Blood Urea Nitrogen Data

| Dog # | BUN1 | Creat1 | BUN2 | Creat2 | BUN3 | Creat3 | BUN4 | Creat4 |
|---|---|---|---|---|---|---|---|---|
| 485-P | 12 | 0.8 | 12 | 0.8 | 12 | 0.9 | 12 | 1 |
| 486-F | 10 | 0.8 | 9 | 0.7 | 12 | 1 | 14 | 1.3 |
| 436-P | 14 | 1.1 | 16 | 1.1 | 17 | 1.1 | 17 | 1.1 |
| 491-F | 11 | 0.8 | 9 | 0.8 | 14 | 1 | 13 | 1 |
| 481-F | 18 | 0.9 | 9 | 0.7 | 13 | 0.8 | 14 | 0.9 |
| 498-P | 8 | 0.7 | 7 | 0.8 | 22 | 1.9 | 52 | 1.9 |
| 484-P | 12 | 0.9 | 8 | 0.7 | 12 | 1 | 16 | 0.9 |
| 451-F | 9 | 0.8 | 8 | 0.7 | 7 | 0.9 | 10 | 0.9 |
| 425-F | 22 | 1 | 9 | 1.1 | 12 | 1 | 15 | 1.1 |
| 455-P | 13 | 1.1 | 10 | 1 | 12 | 1.1 | 12 | 1.2 |
| 502-F | 11 | 1 | 12 | 1 | 16 | 1.1 | 14 | 1.1 |
| 500-P | 13 | 0.9 | 12 | 0.8 | 16 | 1 | 13 | 1.1 |
| 487-P | 14 | 1 | 12 | 1 | 17 | 1.2 | 18 | 1.2 |
| 489-F | 13 | 0.9 | 9 | 0.7 | 13 | 1 | 13 | 1 |
| 448-P | 16 | 1 | 15 | 1 | 17 | 1.3 | 21 | 1.6 |
| 511-F | 11 | 0.9 | 14 | 1 | 15 | 1 | 13 | 1 |

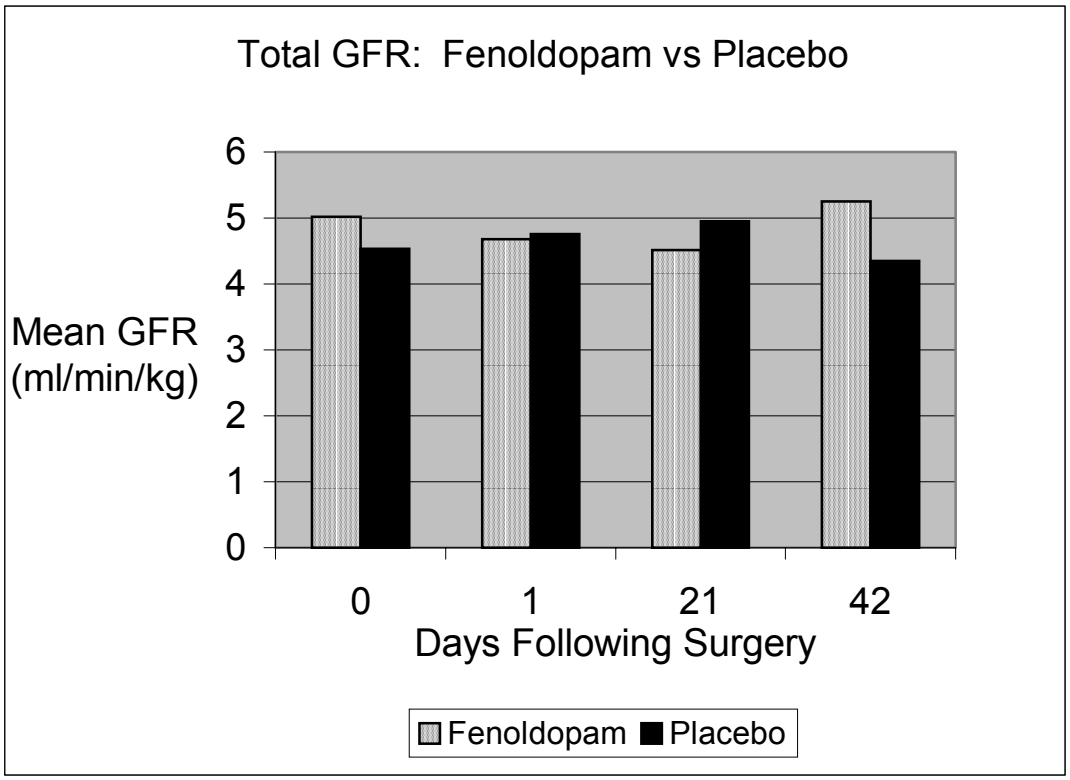
**Graph 3**


Mean BUN: Fenoldopam vs Placebo
Mean BUN (mg/dL)
25
20
15
10
5
0
0
1
21
42
Days Following Surgery
Fenoldopam
Placebo

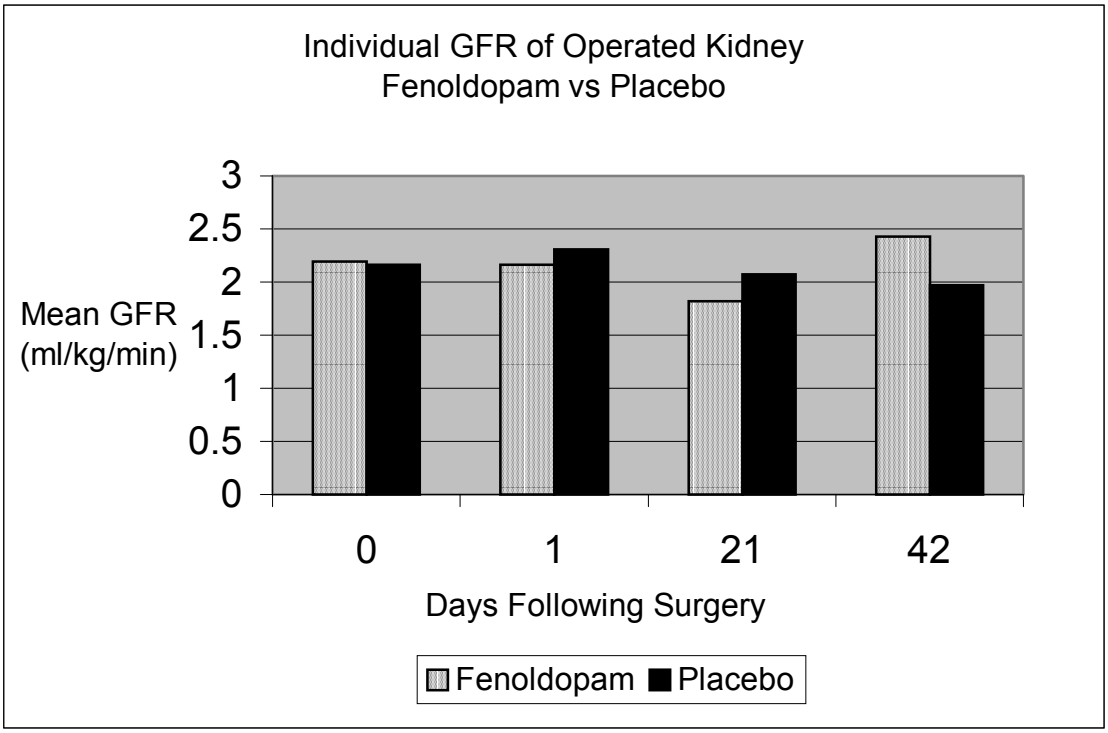
**Graph 4**


Mean Creatinine: Fenoldopam vs Placebo
Mean Serum Creatinine (mg/dL)
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0
1
21
42
Days Following Surgery
Fenoldopam
Placebo

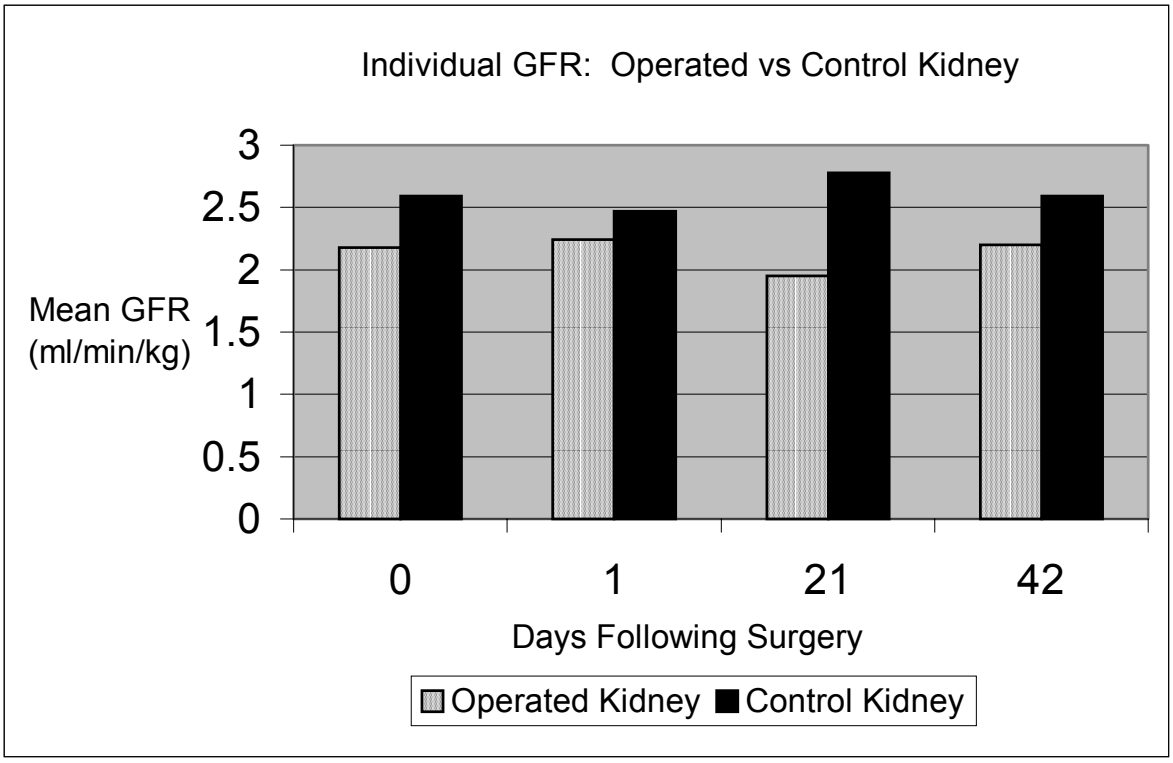
**Graph 5**


Total GFR: Fenoldopam vs Placebo
Mean GFR (ml/min/kg)
6
5
4
3
2
1
0
0
1
21
42
Days Following Surgery
Fenoldopam
Placebo

**Graph 6**


Individual GFR of Operated Kidney
Fenoldopam vs Placebo
Mean GFR
(ml/kg/min)
3
2.5
2
1.5
1
0.5
0
0
1
21
42
Days Following Surgery
Fenoldopam
Placebo

**Graph 7**


Individual GFR: Operated vs Control Kidney
Mean GFR (ml/min/kg)
3
2.5
2
1.5
1
0.5
0
0
1
21
42
Days Following Surgery
Operated Kidney
Control Kidney

## Appendix C

### Abbreviations

| | |
|---|---|
| BP | Blood pressure |
| BUN | Blood urea nitrogen |
| CBC | Complete blood count |
| CRI | Constant rate infusion |
| F | Fenoldopam |
| GFR | Glomerular filtration rate |
| HR | Heart rate |
| MAP | Mean arterial pressure |
| P | Placebo |
| PAH | p-aminohippuric acid |
| PDS | Polydioxanone |
| PSP | Phenolsulphonaphthalein |
| RR | Respiratory rate |
| RBF | Renal blood flow |
| ROI | Regions of interest |
| RVR | Renal vascular resistance |
| SCr | Serum creatinine |
| SNP | Sodium nitroprusside |
| UA | Urinalysis |
| $99^{m}$Tc-DTPA | $99^{m}$ Technetium diethylenetriaminepentaacetic acid |

## Vita

Born, Nancy Lee Zimmerman, at the MacDonald Army Hospital in Newport News, Virginia, Nancy grew up in Monroeville, Pennsylvania and graduated from high school in Fond du Lac, Wisconsin. After graduating from high school, Nancy studied liberal arts for one year at La Sorbonne University in Paris, France, and then returned to the United States to complete her degree. She graduated from the University of Wisconsin-Madison in May 1989 with a Bachelor of Science in Dairy Science. After graduating, Nancy worked as a research assistant and quality control specialist for a dairy genetics improvement facility in Wisconsin. She returned to the University of Wisconsin-Madison to pursue a post-graduate degree in reproductive physiology, but then, matriculated with the UW-Madison School of Veterinary Medicine Class of 1998.

After obtaining her Doctor of Veterinary Medicine, Nancy completed a rotating small animal internship in 1998-1999 at the Virginia-Maryland Regional College of Veterinary Medicine (VMRCVM) in Blacksburg, Virginia, followed by a small animal surgery internship in 1999-2000 at the Dallas Veterinary Surgical Center in Dallas, Texas. In July 2000, she returned to VMRCVM to begin work toward a Master of Science while concurrently working as a resident in small animal surgery. She will complete requirements for both programs in July 2003.