ANIMAL FOR STENTS OR STENTS FOR ANIMALS – AN AREA UNDER CONSTRUCTION (PART II)

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ABSTRACT
The stent used in clinics is broadly classified on the basis of a number of different parameters, however organ based classification is considered in the current part of review literature. A huge amount of literature related to the stenting using animal models available in PubMed has been reviewed over the last 10 years to draw the trend in development and usage of stent in various animal models. This shows that the rate of development in biomedical models is not implemented in clinics due to less awareness and expertise. We hope that the data gathered and sorted in current review may provide a clue to solve the issue of translation of this novel technique.

Keywords: Models for stenting, Veterinary stent, Organ stent and Vascular stent.

INTRODUCTION
Minimally invasive therapeutics in comparison to the traditional open surgical approaches is precise and helps to adhere ‘Tenets of Halsted’. It not only allows maneuvers through small incisional wounds, but also shortens anesthesia time. This prevents self-mutilation in animals due to less pain compared to traditional approaches. Similarly, it needs less handling of tissue, avoiding the chance of infection and contamination both in general and also iatrogenic by reducing the duration of stay in hospital or clinics. In addition, it also renders manipulation at the place, which is inaccessible with traditional surgeries.

In brief if we look at organ-wise stent classification and its use in clinics, it reveals interesting data about which field is less explored or reached clinics.

Esophageal stent
Minimally invasive stents are used in obstructive esophageal cancer of 5-8 diameters, which are difficult to remove through endoscopy [1]. Esophageal stent helps as palliative treatment, which improves patient’s life. However, sometimes it ends with complication known as bird nest deformity [2]. Esophageal strictures treated with stenting allow easy passage for ingesta and less discomfort for the patient and veterinarian, which does not need repeated dilatation. Stenting for esophageal stricture has shown decreased the necessity for repeated interventions in comparison with balloon dilation.

Colonic stent
Usually metallic colonic stents are used to treat benign or malignant Crohn’s stricture, colo-vesical fistula etc. It improves quality of life for patients.

Tracheal stent
Most of small breeds (Apso, Chihuahua, Lhasa, Maltese, Pomeranian, Poodle, Pug, Shih and Yorkshire Terrier) [3] of the canine family suffering from tracheal collapse (intra-thoracic or extra-thoracic) shows symptoms of chronic cough, increasing respiratory efforts.

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and events of dyspnea. Medical management is the
treatment of choice and surgical repair is chosen when
animal do not react well to the treatment. Minimally
invasive approach of endotracheal stenting is a
promising new therapy under trial with challenges of new
complications [4].

In human patients, it has been found with few
complications viz., granulation tissue, stent migration,
stent expectoration, halitosis, mucous retention and mucus
plugging [5]. Whereas in dogs, minor and brief bleeding
[6] that occurred during airway bypass stent placement,
fractured tracheal stent [7].

**Ureteral stent**

Pyelonephritis due to urolithiasis in animals is
very common and mostly undiagnosed due to lack of a
routine checkup. However, this has tremendous potential
to develop progressive chronic kidney diseases, which
may lead to systemic bacteremia and death.

Cats are prone to severe complications after
surgical removal of uroliths (>30%). Post-operative
ureteral stents have been effective in relieving ureteral
obstruction in both dogs and cats with less post-operative
morbidity and mortality [8].

Ureteral stenting is a useful technique to relieve ureteral
stenosis caused due to severe urethral strictures in dog[9]
and cat[10], traumatic penile urethral stricture (in dog)
[11]. However, few complications are need to be
considered while using such techniques viz., risk of
iatrogenic tumor seeding (in dog) [12] intermittent
hematuria (in cat) [13]. Although stenting has a few
hurdles of limitations and complications, in overall it
improves the quality of life in animals having poor
prognosis [14].

A combination of a biocompatible polymer on
metallic stents (tremendous strength), provokes a minimal
immune response when placed into the urinary tract to
maintain ureteral luminal patency [15].

**Urethral stent**

Urethral self-expanding metallic stent (SEMS)
has been an effective tool in obstructive carcinoma of the
feline [16] and canine urethra which significantly
increases the median survival time [17].

**Vascular stent**

Regardless of huge achievement in vascular stent
field compared to other organ stents, it is still limited to
biomedical research and human patients. The important
impediment lies in the early diagnosis of vascular
ailments in animals.

That’s why, although we see that stent field has
been widely explored in research (pig, dog, rabbit and rat
as biomedical models) but very few clinical cases are
performed and reported.

Minimally invasive surgeries (MIS) involve
laparoscopy; thoracoscopy, Endourology and
Interventional Radiology (IR) are a boon for veterinary
field as it relieves quickly, easily and safely. Among these
IR is least invasive methodology of treatment modality
where catheter guided stent delivery has a lion’s share.
Potential applications of catheter guided techniques for
the management of veterinary diseases is boundless. A
number of applications possible using catheter-guided
system is shown in a number of studies viz., pulmonary
valve implantation [18], percutaneous valve stent
insertion to correct the pulmonary regurgitation in sheep
[19].

On Google search, found VET-STENT® series,
which are optimized stents, especially for veterinary
applications. They are self-expanding Nitinol stents in
various sizes and designs. Three different models
available (trachea, inferior vena cava and urethra) are
compatible with magnetic resonance (MR) [20]. It shows
that stent field is yet to not reach to the clinic as common
as expected due less commercial involvement.

**Experimental Studies**

A number of animals are being used for
experimental and preclinical studies of vascular and organ
stents but most commonly used animals are dog, rabbit
and pig. Use of biomedical models in preclinical studies
has added an enormous amount of information about
different stents. We scanned articles on PubMed for last
10 year and found 1308 articles published online
regarding stent experiments using animal models. After
sorting them, plotted graphs per year as per species used,
material used, organ targeted or eluting drug for last 10
years in four graphs (Graph 1-3).

Interestingly, it seems that porcine model uses a
lot followed by rabbit in stent research. Again, bio-
absorbable material as base material for stent is increasing
compared with BMS (bare metal stent) mostly steel or
cobalt chromium. Eluting drugs area common trend and
accepted method, which has revolutionized the whole
field. Starting from simple antithrombotic drugs,
antimitotic drugs till nanoparticles, stem cells, and
antibodies have been tried as eluting material in stents.
However, sirolimus and paclitaxel are often used as
standards in many studies. Most of this stent research has
been carried out in the vascular field as it’s more demanding
for humans (Graph 1-3).

Canine (dog) model has been used in many
cardiovascular stent evaluation studies more often in
China, Korea, USA, Japan and Spainare to name among
the few. Stenting has been performed in bile duct [21],
coronary artery [22], larynx [23], tracheal lumen [24],
bronchus [25], esophagus [26], AVF, jugular vein, carotid
artery [27], (Abdominal/infrarenal/ thoracic) aorta [28],
renal artery [29], deep femoral artery [30], iliac artery
[31], portal vein [32], urethra [33], pancreas [34].
Swine (pig) model has been used for a very long time, mostly in USA, Germany, China, Japan, Canada, Brazil, Finland, Switzerland, Belgium and many others, however now a days a trend of using mini-pigs are more practical and economical for long-term experiments. The number of researchers have used the pig as a biomedical animal model for number of organ stents e.g. pancreatico-biliary tree [35], coronary artery [36], esophagus [37], AVF, jugular vein, carotid artery [38], (Abdominal/infra-renal/thoracic) aorta [39], renal artery [38], iliac artery [40], ureter [41], bronchus [42], portal vein [43], deep femoral artery[44], colon [45], lung [46], aortic valve [47].

Rabbit and rat model require relatively challenging skills, especially in vascular stenting experiments due to its size and type of models used possible procedural complication (Fig.1& Table 1). However, they are preferred due to cost-effective and easy in handling. Models used in different part of the world (especially in Turkey, India, China, Korea, China, Japan, Taiwan, Canada are to name among the few) for different organs viz. Bile duct [48], external iliac arteries [49], urethra [50], esophagus [51], jugular/carotid vessels [52], knee joint [53], aorta [54] and ureter [55].

Similarly, in rat models, different stent have been used (especially in Korea, Italy, USA and Australia to name among the few) for different sites or organs e.g. Intestine [56], aorta [57], ureter [58], esophagus [59], trachea [60], urethra [61], carotid [62], subcutaneous [63], portal vein [64] and pancreas [65].

All these models are used to evaluate the efficacy and compatibility of newly developed stents either for humans or animals (mostly for human use). Evaluation can be from day 7 till years; however, mostly few months have been considered enough to predict long term effects in human. This is due to small life span and rapid vascular response in animals compared to human. Swine model is mostly used due to its resemblance with human lesions in terms of vascular response. Cats have not proven to be a broadly suitable model due to atheromatous lesion is different distribution and characteristics. Since, cat is a good model for biliary ailments (represent biliary problems similar to human), so can be considered as an ideal model for biliary stenting as well.

Neither have dogs been extensively used in atherosclerosis research, although widely used in cardiovascular and surgical studies. Hypothyroidism must be induced to overcome the natural resistance of dogs to hypercholesterolemia or lesion development. Rabbit are used for lesion characterization, drug interactions and mechanical arterial injury due to economy, size (enough big to operate or evaluate comfortably), shorter duration for disease-induction, availability and ease in handling and rat are used due to their small size, possibility of easy monitoring and using controlled parameters in mechanistic study (knockout animals) however rodent model in general, has disadvantage of different lipoprotein profiles to man and smaller vessel size. Smaller vessel sizes not only results in different arterial wall morphology, but also difficult to perform certain surgical interventions viz., balloon catheterization [66].

Evaluation of stent in model

Usually, animal study provides lesions much faster depending on species, breed, nutrition and type of model. Location of implanted stent matters in the in vivo monitoring of stent. Implanting procedure and handling of stented vessel samples during retrieval are vital to the lesions observed in stenting experiments. A proper guideline [67] need to be considered in evaluation results of stenting in experimental models, which are vital for future clinical implantation during this stent war (too rapid progress to evaluate). A wide variety of parameters can be considered for evaluating efficacy, however, most common are neointimal hyperplasia (NH), luminal narrowing (LN), (apparent) re-endothelisation (RE), peri-strut inflammatory response (PIR), internal elastic lamina disruption (ILD) and non-obstructive peri-strut fibrin (NOPF) as used in our previous experiment(Graph 4) to evaluate stent efficacy [68, 69].

From bench to bedside

Few of the published works (30 publications) found on PubMed, is cited in this article, however, there is much more data and cases done all over the world which are not reported or documented. Especially in India, where we need to deal with urological cases much more than the rest of the world. In such cases, we required to focus on better quality of treatment and better quality in the life-style of the animal. We believe that the huge number of challenging cases involving tracheal, urological and udder injuries in caprine and bovine species will get help from stenting field, quite soon.

Most of the reported cases are either performed in canine or feline, largely in USA (Table 2). Few techniques have been used in piscis and birds e.g. A case of subcutaneous emphysema resolved in a Griffon Vulture chick (Gyps fulvus) using stent[70].Previously, stent was used as scaffolding device to support stenosed hollow tissue, which has later added with the treating of weak, tear, defective, damaged cancerous tissues. Stent has also been used for ablation of benign lesions or malignant tumors of hollow viscera using radiofrequency ablation from gastrointestinal, biliary, and urinary tract [71]. Earlier, it was used only as anaphylaxis, but nowadays, it is used as prophylaxis e.g., prophylactic after gastro-duodenostomy [72].

In a nutshell, use of stent either organ or vascular can become a clinical routine only if the knowledge gained in preclinical research and clinical cases of major universities is put together with commercial investors.
Stenting/Percutaneous approach has been shown advantages in a number of cases, including: (i) Oncological cases (Trans-arterial chemoembolization or palliative radiotherapy or chemotherapy of neoplastic diseases of vital tissue or organs, Stenting of malignant urethral or ureteral obstruction. Stenting for stenosed lumens due to malignancy in vessels, airway, gastrointestinal tract, where open surgery is contraindicated). (ii) Nutritional cases (Placing naso-jejunal feeding tube, percutaneous gastrostomy tube, percutaneous gastrojejunosotomy tube, esophago jejunosotomy tube) (iii) Urinary cases (Tube / stent placement for as percutaneous nephrostomy tube, ureteral or urethral stent for urolithiasis traumatic disruption or iatrogenic or malignant obstruction.) (iv) Mixed cases (Foreign body removal in vessels, trachea or bronchi; Glue embolization of hepatic arterio-venous malformations, thoracic duct, biliary drainages, nasal epistaxis. Stenting in esophageal stricture, repair of complex vascular malformations, balloon peri-cardiotomy for recurrent pericardial effusion. In-dwelling drainage catheters with subcutaneous access port) [73]. Also, if the value issue and training aspects are taken care, no sooner it will be enforced in companion than in farm animals.

Stent war

The rate at which the stent market is expanding in general, it has become a challenge to track and implement it in the veterinary field or the medical field. It is very important to evaluate a product well before being used so demands active research in veterinary, which is lacking. The irony of the field is, animal models are extensively used to evaluate every product of stent used in medical (human) field, but hardly very few products are available for use in the veterinary field.

The risks related to DES placement are marginal compared to the untreated stents or conventional methods of treating the diseases with conventional therapy involves dual systemic therapy carrying several disadvantages e.g. Irregular dose and dosage to the targeted site, side effects, contraindications, high grade responsibility, exasperating follow-up treatment, uncertainty and unreliability. Recent literature concerned with coated stents shown a diminished rate of occlusion (stenosis), thrombosis and even reduced the requirement of systemic medication and follow-up.

Many stenting procedures need advanced imaging modalities, however; fluoroscopy could be a vital tool for most of the stenting procedures. In stenting, an array of guide wires with numerous properties. Stenting catheters are specifically tailored for specific procedures, stents composed of various materials and designs, which replaces the quality of surgical pack. It is ought to be noted that several of the already developed veterinary stenting procedures might end in vital hurt or maybe death, without prior experience.

Table 1. Complications in vascular stenting in rabbit model of antegrade-iliaic stenting

<table>
<thead>
<tr>
<th>Rabbits (n)</th>
<th>Post Mortem Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Anaesthetic over dosage and stress leading to dyspnoea and death.</td>
</tr>
<tr>
<td>2</td>
<td>GW injury in heart.</td>
</tr>
<tr>
<td>1</td>
<td>Blood loss due to slippage of carotid artery ligature during post stenting.</td>
</tr>
<tr>
<td>1</td>
<td>GW injury in external iliac artery</td>
</tr>
<tr>
<td>1</td>
<td>GW injury resulted in internal bleeding and rupture of posterior aorta as a result of loop formation of GW due to deployment of one of the stent at branching of posterior aorta</td>
</tr>
<tr>
<td>1</td>
<td>Excessive haemorrhage during angiography</td>
</tr>
<tr>
<td>1</td>
<td>Blind stenting (Tripping of electric supply) resulted in intussusception and rupture of iliac artery due to incomplete stent deployment at 6 atm pressure.</td>
</tr>
</tbody>
</table>
Table 2. Few clinical cases of stenting in animals reported as publication (A-G)

<table>
<thead>
<tr>
<th>Clinical cases of stenting</th>
<th>Country</th>
<th>Location</th>
<th>Material</th>
<th>Species</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Esophageal stents</strong></td>
<td>UK</td>
<td>Single cervical esophageal stricture</td>
<td>Biodegradable self-expanding</td>
<td>Feline</td>
<td>[74]</td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td>Esophageal squamous cell carcinoma</td>
<td>Self-expanding metallic stent</td>
<td>Canine</td>
<td>[75]</td>
</tr>
<tr>
<td></td>
<td>Germany</td>
<td>Single cervical esophageal stricture</td>
<td>Self-expanding metallic stent</td>
<td>Feline</td>
<td>[76]</td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td>Benign esophageal stricture</td>
<td>Balloon dilatation only</td>
<td>Canine, Feline</td>
<td>[77]</td>
</tr>
<tr>
<td><strong>B. Colonic stents</strong></td>
<td>USA</td>
<td>Colorectal neoplastic obstruction</td>
<td>Nitinol stent</td>
<td>Canine</td>
<td>[78]</td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td>Colonic adenocarcinoma</td>
<td>Self-expanding metallic stent</td>
<td>Feline</td>
<td>[79]</td>
</tr>
<tr>
<td><strong>C. Tracheal stents</strong></td>
<td>USA</td>
<td>End stage tracheal collapse</td>
<td>Nitinol</td>
<td>Canine</td>
<td>[80]</td>
</tr>
<tr>
<td></td>
<td>Spain</td>
<td>Tracheal collapse</td>
<td>--</td>
<td>Canine</td>
<td>[4]</td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td>Tracheal collapse</td>
<td>Nitinol</td>
<td>Canine</td>
<td>[81]</td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td>Tracheal collapse</td>
<td>Nitinol</td>
<td>Canine</td>
<td>[82]</td>
</tr>
<tr>
<td></td>
<td>Korea</td>
<td>Obstructive diseases of trachea</td>
<td>Silicone</td>
<td>Canine</td>
<td>[83]</td>
</tr>
<tr>
<td></td>
<td>Canada</td>
<td>Tracheal collapse</td>
<td>Nitinol</td>
<td>Canine</td>
<td>[84]</td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td>Tracheal collapse</td>
<td>Nitinol</td>
<td>Equine</td>
<td>[85]</td>
</tr>
<tr>
<td><strong>D. Nasopharyngeal stents</strong></td>
<td>USA</td>
<td>Bilateral bony choanal atresia</td>
<td>Temporary stenting</td>
<td>Feline</td>
<td>[86]</td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td>Nasopharyngeal stenosis</td>
<td>Metallic stent</td>
<td>Feline</td>
<td>[87]</td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td>Recurrent nasopharyngeal stenosis</td>
<td>(2-cm) braided-wire endoprosthesis</td>
<td>Feline</td>
<td>[88]</td>
</tr>
<tr>
<td><strong>E. Esophageal stents</strong></td>
<td>Japan</td>
<td>Carcinoma of bladder neck and prostate</td>
<td>Normograde fashion via percutaneous puncture</td>
<td>Canine</td>
<td>[12]</td>
</tr>
<tr>
<td></td>
<td>Italy</td>
<td>Ureterotomy/Ureteroliths removal surgery</td>
<td>3 French double-J catheters</td>
<td>Feline</td>
<td>[10]</td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td>Proximal ureteral stenosis</td>
<td>2 double-pigtail ureteral stents</td>
<td>Canine</td>
<td>[89]</td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td>Intra-corporeal lithotripsy / Ureteral calculi</td>
<td>A 4.8-Fr, 26-cm double-pigtail ureteral stent</td>
<td>Pisces (dolphin)</td>
<td>[90]</td>
</tr>
<tr>
<td><strong>F. Urethral stents</strong></td>
<td>Korea</td>
<td>Post-surgical urethral stricture</td>
<td>SEMS with ePTFE*</td>
<td>Canine</td>
<td>[9]</td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td>Traumatic urethra rupture</td>
<td>SEMS</td>
<td>Feline</td>
<td>[13]</td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td>Traumatic stricture of penile urethra</td>
<td>SEMS, Nitinol coating</td>
<td>Canine</td>
<td>[11]</td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td>Urethral obstruction secondary to transitional cell carcinoma (TCC).</td>
<td>SEMS, Nitinol coating</td>
<td>Canine</td>
<td>[14]</td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td>Obstructive carcinoma</td>
<td>SEMS</td>
<td>Canine</td>
<td>[17]</td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td>Malignant urethral obstruction</td>
<td>Balloon expandable metallic stent</td>
<td>Canine</td>
<td>[91]</td>
</tr>
<tr>
<td></td>
<td>Australia</td>
<td>Malignant urethral obstruction</td>
<td>SEMS</td>
<td>Feline</td>
<td>[16]</td>
</tr>
<tr>
<td></td>
<td>Korea</td>
<td>Refractory lower urinary tract obstruction</td>
<td>SEMS</td>
<td>Feline</td>
<td>[92]</td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td>Malignant urethral obstruction</td>
<td>SEMS</td>
<td>Feline</td>
<td>[93]</td>
</tr>
<tr>
<td><strong>G. Caval stents</strong></td>
<td>USA</td>
<td>Venacava</td>
<td>Caudal vena caval obstruction</td>
<td>Feline</td>
<td>[94]</td>
</tr>
</tbody>
</table>
Graph 1. Species-wise stent publications

![Species-wise stent publications graph](image1)

Graph 2. Year-wise research in eluting stents

![Year-wise research in eluting stents graph](image2)

Graph 3. Organ-wise stent publications

![Organ-wise stent publications graph](image3)

Graph 4. Graded histological endpoints for evaluation stent (DDES) patency and tissue related response in rabbit model

![Graded histological endpoints graph](image4)

REFERENCES


