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Balloon Assisted Maturation (BAM) of the Arteriovenous Fistula: the Good, the Bad and the Ugly!

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INTRODUCTION

Arteriovenous fistulae (AVF) are the preferred mode of dialysis vascular access due to low long-term rates of infection and stenosis.^{1–3} In addition, patients with a functioning AVF live longer and cost less as compared to patients dialyzing through a tunneled dialysis catheter.^{4–10} Indeed, the main reason for the increased mortality of US dialysis patients as compared to patients in Europe appears to be ascribable to differences in facility vascular access use (more tunneled dialysis catheters [TDCs] and fewer AVFs in the United States).¹¹

In view of this data, there has been an aggressive push to increase the number of AVFs placed in this country (Fistula First), which has increased AVF prevalence rate from 24% in 2003 to 60.4% currently.^{9,12,13} Despite the many advantages of the native AVF, a number of studies have documented major problems with AVF maturation (failure to increase flow and diameter adequately to support dialysis)^{14–18} as a result of a peri-anastomotic venous segment stenosis.^{19–21} In addition, it is possible that the rate of AVF maturation failure has increased following the Fistula First initiative since more AVFs are now perhaps being created in patients with marginal veins (arterial diameter < 2mm and venous diameter < 2.5–3mm), who would previously have received PTFE grafts.²² To place the magnitude of the problem in perspective, 60% of created AVFs were not suitable for dialysis at between 4–5 months post surgery in the large, multi-center, National Institutes of Health funded, Dialysis Access Consortium study.¹⁶ In addition, another recent study suggested a primary failure

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rate of almost 40%.²³ This high rate of AVF maturation failure has likely resulted in a prolonged duration of TDC usage (80% of incident hemodialysis patients start dialysis with a catheter), with all of its attendant complications (infection, thrombosis and central vein stenosis).^{5,9}

The Kidney Disease Outcomes and Quality Initiative (K-DOQI) guidelines for this problem suggest that the AVF needs to be examined at 4–6 weeks post surgery by a qualified individual and then referred as needed for angioplasty and/or surgery.²⁴ Using this paradigm, a number of authors have reported their results on the use of angioplasty in particular, to treat the peri-anastomotic stenoses responsible for AVF maturation failure.^{20,21}

More recently, a number of physicians have championed a more aggressive approach to AVF maturation failure in which repeated long segment angioplasty procedures (Balloon Assisted Maturation [BAM]) are used to sequentially dilate up the peri-anastomotic venous segment, converting it at times into a “collagen tube”. Of note, this aggressive angioplasty approach is often combined with the use of coiling or percutaneous ligation to direct flow down the most direct pathway to the central circulation.^{25,26} In addition, recent papers have described the use of intra-operative “primary balloon angioplasty” at the time of surgery which could allow for AVFs to be created in patients with small arteries and veins (artery < 2mm and vein < 2.5mm).^{27,28}

OBJECTIVE

The goal of this review is to perform a scientific evaluation of the available data on balloon assisted maturation (BAM). In order to do this we plan to divide this review into three main sections. We will initially describe the pathology and pathogenesis of AVF maturation failure with a focus on the biology of this process. We will then summarize the available data on BAM (both procedural and outcome), with a special emphasis on the pros and cons of this procedure. Finally, we will try and combine all of this information to assess whether BAM could be a useful addition to the armamentarium of choices (or lack of choices), currently available for the management of AVF maturation failure.

PATHOLOGY AND PATHOGENESIS OF AVF MATURATION FAILURE

At a radiological level, AVF maturation failure is characterized by a peri-anastomotic venous segment stenosis as shown in Fig 1a. At a biological level, we have described an aggressive venous neointimal hyperplasia in subjects with AVF maturation failure (Fig 1b); which is comprised primarily of myofibroblasts, which have likely migrated in from the media or perhaps even the adventitia.¹⁹ In addition to this aggressive neointimal hyperplasia it is likely that AVF maturation failure is also associated with a lack of appropriate outward remodeling or perhaps even a degree of negative or inward remodeling (Fig 2).^{3,29,30} At a pathogenetic level it is likely that vascular injury is the initiator of both these processes (neointimal hyperplasia and a lack of outward remodeling). Specific mediators of vascular injury in the setting of AVF maturation failure include (a) direct hemodynamic injury due to non-laminar flow and oscillatory shear^{31–37} (b) surgical injury from suture site inflammation and the handling of the peri-anastomotic venous segment^{3,29,30} (c) possible twisting and torquing of the venous segment at the time of AVF creation.³⁸

In addition, we and others have previously documented the presence of a significant amount of neointimal hyperplasia in venous segment samples collected prior to surgery (before the initiation of hemodynamic and surgical injury), suggesting that uremia, inflammation and oxidative stress could be causing endothelial dysfunction resulting in neointimal hyperplasia, even prior to actual AVF creation³⁹ (Fig 3). This could be a particularly relevant finding since subjects with poor endothelial function due to uremia may respond very poorly to the very significant direct endothelial injury that occurs in BAM.

BALLOON ASSISTED MATURATION

(a) Procedure

The fundamental concept behind balloon assisted maturation is that repeated aggressive balloon angioplasty with disruption of the venous wall layers, rather than being detrimental to the AVF as a result of vascular injury; could actually be beneficial in that it converts an inadequate AVF created out of marginal vessels into a good sized “collagen tube”. An important technical aspect of the procedure is to dilate up the venous outflow which has a direct line access into the upper arm cephalic or basilic system, while at the same obliterating other collaterals (accessory veins) through percutaneous ligation or coiling techniques.^{25,26,40} Another intriguing aspect is the preferred use of controlled venous rupture during angioplasty in many instances in order to generate fibrous tissue around the AVF.²⁷ More recently a number of authors have described the use of primary balloon angioplasty at the time of surgery to dilate veins as small as 1–1.5mm prior to creation of an AVF, followed by BAM.^{27,28}

(b) Outcomes

Miller et al. have described some initial data, in which 122 patients who were seen for inadequate maturation of the AVF were divided into two groups. Group I comprised patients with large diameter (5–8mm) but deep (>6mm below the skin) AVFs at presentation while Group II comprised AVFs with small diameters at presentation (2–5mm). Maturation was successfully achieved in 118/122 patients using sequential balloon assisted maturation (BAM). Group I and II patients required a mean of 1.6 and 2.6 procedures respectively to achieve maturation with a mean time to maturation of 5 and 7 weeks respectively. The three month post intervention unassisted primary patency's in these two groups, was 47% and 49% respectively, with 1 year figures of approximately 15% for both groups. The one year secondary patency's were 72% and 77%.²⁵ The number of post-maturation angioplasties per year in order to maintain future patency was not provided. Miller and colleagues more recently, described the use of aggressive balloon assisted maturation in 140 consecutive patients with thrombosed AVFs.²⁶ 85% of the AVFs were successfully declotted and 79% became usable for hemodialysis. Following thrombectomy, an average of 2.6 angioplasties/0.34 stent placements/0.22 coil placements were required for the AVF to mature. Post-maturation maintenance required an average of 2.78 interventions (including 0.52 thrombectomies) per access year. The post maturation primary unassisted patency in this study was 53% at 3 months, with a 12 month secondary patency of 90%. De Marco Garcia et al. have described data from 62 primary balloon angioplasties in 55 patients followed by BAM. 85% of their patients were able to achieve maturation and the one year secondary

patency was approximately 80%.²⁸ In a larger series, Chawla et al.²⁷ have described rapid AVF maturation (estimated maturation period of 53 days) using aggressive angioplasty, which caused significant injury to the venous segment. They have hypothesized that this injury (which includes hemorrhage as a result of controlled venous rupture) could be responsible for the remodeling of the venous segment into a large diameter fibrous tube, which could mature more rapidly and also be more resistant to cannulation injury as compared to AVFs that mature in the conventional fashion.

PROS and CONS

The main advantage of BAM is that an AVF can be surgically created, regardless of arterial and venous diameters (venous mapping becomes redundant!) and then handed over to the interventionalist for repeated angioplasties to allow for clinical maturation. Does the procedure work? The answer to this has to be a resounding “Yes”! All the groups described above, were able to achieve maturation (although this was not formally defined) in the vast majority of patients that were referred to them. In addition, their data suggest that the time to AVF maturation was perhaps better as compared to conventional angioplasty approaches.^{20,21}

The main clinical benefits of BAM with or without primary balloon angioplasty, therefore are that it could:

- Greatly expand the pool of patients who would be suitable for an AVF since patients with 1–2 mm diameter arteries and veins could end up with a mature AVF through a combination primary balloon angioplasty and the BAM procedure.
- Significantly reduce the duration of TDC placement and its attendant complications in patients who start hemodialysis with a TDC; by reducing the maturation time.
- Potentially avoid TDC placement altogether, as a function of the rapid time to maturation in patients who receive a pre-emptive AVF.
- Allow for the development of a large diameter and more fibrous AVF (due to repeated episodes of injury followed by healing), which might be easier to cannulate and also be more resistant to cannulation injury, with potentially a requirement for a lesser degree of cannulation skills.

On the other hand there are a number of significant negatives of the BAM procedure in the broad areas of biology, morbidity, economic cost and a lack of well-defined outcomes.

- **Biology:** Over three decades of research on the mechanism of action of angioplasty does not support the underlying thesis of BAM. Angioplasty works by causing an aggressive outward remodeling through intima-media rupture. In doing so it also causes significant endothelial and smooth muscle cell damage, and the vessel wall invariably responds with an aggressive neointimal hyperplasia.^{41–43} While most of the data on angioplasty induced neointimal hyperplasia comes from a study of arterial based models it is very unlikely that there will be no response to injury in the venous system; especially a venous system which has intrinsically high baseline levels of inflammation and oxidative stress as a result of the uremic milieu;^{44–46}

with in many cases, pre-existing neointimal hyperplasia.³⁹ In support of this we have demonstrated a reduction in cumulative AVF survival (from the time of successful maturation onwards), in patients who required two or more angioplasties for their AVF to mature as compared to those who required no interventions.⁴⁷ In addition, at a more biological level, Chang et al.⁴⁸ have documented cellular proliferation within neointimal lesions following angioplasty of an AVF as compared to the extent of proliferation within the neointima of AVFs. that failed after surgery without undergoing additional angioplasty injury

In addition, while the concept of creating a collagen tube is both unique and innovative, the lack of a layer of endothelial cells lining this collagen tube casts doubts, at least from the vascular biology standpoint on the durability of this approach (see outcomes below). Specifically, if the collagen tube behaves perhaps like a PTFE graft then why not just put in a PTFE graft (preferably an early stick graft), instead of going down the pathway of BAM. On the other hand if the collagen tube behaves like a well functioning AVF then clearly this is worth it for the reasons described above (in the advantages) and those below (see outcome, economics and morbidities).

- **Outcomes and Economics:** In order for BAM to become a well accepted standard of care intervention it is essential that we collect more data on outcomes. Thus while all the groups who have pioneered this approach are to be congratulated on their aggressive approach to the intractable problem of AVF non-maturation, we still need to collect hard data on the natural history of an AVF that has undergone assisted maturation using the BAM approach, and is currently being used for hemodialysis. If such an AVF continues to require an angioplasty every 3 months (at a cost of \$3,000 – \$4,000 per angioplasty in an extension of practice setting) then BAM is perhaps not the right thing to do either at an individual patient level (see co-morbidities below) or at a health economics level. On the other hand, if this AVF requires very few further interventions for long-term success; then clearly the initial expenditure of time, effort and money is well worth it. In other words: “How Many is Too Many (Fig 4)?”

The initial data from Miller et al. suggests the need for almost three interventions per post maturation access-year, although the actual numbers of patients is very small after 6 months. Importantly, a rough economic analysis performed by Miller suggests a benefit of the BAM procedure as compared to the placement of a new access.²⁶ This analysis does not, however, take into consideration, the increased costs of the larger number of post maturation angioplasties in the BAM group; which would not be covered within the standard yearly costs for hemodialysis with an AVF versus a TDC as described in their manuscript.²⁶

- **Morbidity:** CKD and ESRD patients have a huge burden of comorbidity which results in multiple out-patient clinic and hospital visits, and while not impossible, the multiple angioplasties (both prior to and after maturation) with potential complications, clearly place an additional burden on these patients; albeit a burden that is well worth carrying if the outcomes (survival and cost) are good (see above).

In summary, we do agree that BAM with or without primary balloon angioplasty is an innovative, albeit aggressive approach to the important clinical problem of AVF maturation failure. It needs to be emphasized that there are currently no effective therapies for this problem and all the groups that have pioneered this approach therefore need to be credited for their attempts to find a solution to this problem.

Despite the initial enthusiasm for this procedure within some groups, however, it needs to be emphasized that the basic thesis for this approach at a biological level goes against everything that we know about the vascular response to injury; although it is possible (albeit unlikely) that the high flow venous segment in the setting of an AVF is a very different beast as compared to endothelial and smooth muscle cell injury in an arterial setting (personal communication; Dr. Greg Miller).

The answer as always, lies in the urgent need for a well designed, randomized clinical study which compares BAM with or without primary balloon angioplasty as needed, against a conventional approach to AVF maturation. We believe that this is the only way to truly assess the benefit (or otherwise) of this procedure on a variety of outcomes (patency, morbidity and cost). We do understand, however, that the conduct of such a study will not be easy; not least because of the current lack of consensus on what is a “conventional approach” to AVF maturation.

Another, perhaps complementary approach, to a randomized study would be to attempt to identify patient subsets that do not require continuing angioplasties following successful BAM. This would likely require a detailed survey of both clinical *and* biological predictors in patients being treated by BAM. For example, it is possible that patients with good endothelial function (large increases in diameter with flow mediated dilatation) and small vessels, comprise the particular subset that would benefit most from BAM.

Finally, there has recently been a plethora of reports on local therapies that can be applied at the time of balloon angioplasty of the vascular access, which may reduce post angioplasty restenosis. These include the use of paclitaxel coated balloons⁴⁹ and stents,⁵⁰ as also the delivery of drugs such as dexamethasone to the adventitia using an endovascular approach (placement of a sheathed balloon with a microsyringe that pierces through the vessel wall at the site of angioplasty). It is possible that combining BAM with the local therapeutic application of an anti-stenotic agent could result in a win-win situation; namely the creation of mature AVFs in patients with small vessels, without the need for multiple post-maturation angioplasties!

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Fig 1. Arteriovenous Fistula Maturation Failure; from Radiology to Histology

Figure 1a describes the classical radiological picture of AVF maturation failure, characterized by a tight peri-anastomotic stenosis. Tissue from the stenotic area when looked at under a microscope reveals the typical histological picture of AVF maturation failure; an aggressive neointimal hyperplasia probably in combination with a lack of appropriate outward remodeling. (black double headed arrow = thickness of neointimal hyperplasia; red thin arrow = possible direction of migration of myofibroblasts and smooth muscle cells; broad red arrows = lack of appropriate outward remodeling or alternatively inward remodeling; white bar = medial thickness)

Fig 2. Luminal Stenosis is the final end result of both neointimal hyperplasia and inappropriate remodelling

The top panel describes a complete lack of stenosis even in the presence of vessel wall thickening due to a significant degree of outward remodeling. The lower panel documents the presence of significant luminal stenosis with minimal vessel wall thickening, because of inward (instead of outward) remodeling.

% Stenosis	46.6 ± 9.3
I/M Area Ratio	0.24 ± 0.07
Average IM Thickness	0.34 ± 0.12
Maximal IM Thickness	1.16 ± 0.30

Fig 3. Pre-existing Neointimal Hyperplasia

Note the very significant amount of neointimal hyperplasia present even prior to vascular access creation. This suggests that oxidative stress and inflammation as a result of uremia could result in endothelial dysfunction and subsequent neointimal hyperplasia which is not linked at all to hemodynamic and surgical injury.

a

b

Fig 4. How Many is Too Many?

Fig 4a describes the requirement for three angioplasties prior to successful maturation. Once mature, however, no further interventions are needed and the blood flow within the AVF continues to increase. In marked contrast **Fig 4b**, describes a clinical setting in which once again three angioplasties are required to achieve AVF maturation. Post maturation patency, however, necessitates an angioplasty every 3 months. We suggest that the additional time, effort and money that will be spent on post-maturation angioplasties, argues against balloon assisted maturation in many instances.