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FairEmbo concept for arterial embolizations: In vivo feasibility and safety study with suture-based microparticles compared with microspheres

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Compliance with Ethical Standards:

1. Funding: This study was not supported by any funding
2. Conflict of Interest: The authors declare that they have no conflict of interest.
3. Ethical approval: All applicable international, national, and/or institutional guidelines for the care and use of animals were conducted. All procedures performed in studies involving animals were in accordance with the ethical standards of the institution or

practice at which the studies were conducted (agreement of the Committee of Ethical Animal APAFIS#14851-2018042610172296).

4. Informed consent: For this type of study informed consent is not required.
5. Consent for publication: Consent for publication was obtained for every individual person's data included in the study.

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FairEmbo concept for arterial embolizations:

In vivo feasibility and safety study with suture-based

microparticles compared with microspheres

ABSTRACT

Purpose: Microspheres are effective embolic agents especially for the management of bleeding and oncologic lesions. The first FairEmbo study reported the effectiveness of embolization using suture fragments. The effectiveness and safety of arterial embolization with Suture-Based Microparticles (SBM) were assessed in a swine model.

Materials and methods: In this ethical-approved animal study, a polar artery in each kidney was embolized in four swine: one side with hand-cut non-absorbable SBM (Flexocrin 2[®]) and the contralateral side with Embozene[®] 900 for comparison. Swine were followed for 3 months (M3) to evaluate the effectiveness and the safety of SBM. Follow-up protocol included clinical monitoring, computed tomography (CT) control and digital subtraction angiography (DSA), followed by histological analyses. The SBM confection parameters were evaluated by automatic microscopic sizer. RStudio software and Mann-Whitney test (significance at $P<0.05$) were used for statistics.

Results: The average size of SBM was 1002 μ m (SD=258). All targets were effectively embolized by SBM, with an angiogram defect estimated at 45.6% (95% CI [35.9-55.2]), compared to 40.5% (95% CI [30.6-55.5]) for Embozene[®] group, without significant difference ($P=0.342$). The average duration of SBM embolization procedure was significantly increased compared to Embozene[®] embolization (1202s versus 222s, $P=0.029$). There were no statistical differences in M3 DSA and CT for SBM and Embozene[®], with persistence of partial arterial occlusion and atrophic embolized area. No postoperative complications were observed on clinical and CT controls.

Conclusion: This experimental study suggests that embolization with SBM is safe and effective in short and medium-term follow-up as compared to microspheres.

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- 7 **No level of evidence**
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KEYWORDS

- Distal embolization
- Microspheres
- Suture-Based Microparticles
- Embozene®
- Emerging countries

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INTRODUCTION

While endovascular embolization is being increasingly performed in developed countries, it has become technically challenging for low- and middle-income countries to adopt these interventions in clinical practice, with significant implications for health-care system [1, 2]. For the latter, embolization procedures remain scarce for many supposed reasons: affordability in a financially-constraint system, a limited access to hospitals and trained physicians, the lack of a supplying network of embolic agents

The lack of resources may be responsible for a significant increase of morbidity and mortality [1-6].

Therefore, the FairEmbo concept was created in an atypical approach and it seeks to make embolization procedures accessible by solving the problem of the availability of embolization agents. The first FairEmbo study reported the feasibility, effectiveness and safety for proximal embolization using homemade and extemporaneously torpedo-form embolic agents from absorbable and non-absorbable suture fragments of 1 to 2 cm [7]. This was confirmed by a recent clinical case report, showing effective hemostatic embolization of a renal artery pseudoaneurysm using absorbable torpedo-form suture fragment [8].

The use of microspheres as embolic agent has been widely adopted for distal embolization procedures [9-13]. Unfortunately to date, the expediency for emerging countries to treat patients with calibrated microspheres or PVA particles embolization remains limited. In this context, the use of inexpensive and available homemade microparticles should be noteworthy. If sutures can be shaped and injected throw a catheter into small particles, the latter should be thought to be used in the various indications mentioned above.

Within this dynamic context, this study aims to evaluate the shaping Suture-Based Microparticles (SBM) and its feasibility, effectiveness and safety for arterial embolization in a swine model, compared to microspheres.

MATERIALS AND METHODS

Animal experiments

Four Pietrain pigs (40 +/- 5 kg) were used after agreement of the Committee of Ethical Animal (APAFIS#14851-2018042610172296), in accordance with the institutional and national guidelines. During the procedures, induction of anesthesia was obtained by 2 mg/kg propofol and maintained with gaseous sevoflurane (2%) under mechanical respiration (Dräger Zeus®, Dräger Inc., US).

Suture-based microparticles (SBM)

A nylon non-absorbable monofilament suture (Flexocrin®, B. Braun, Germany) sizes 2 USP (United States Pharmacopeia), equivalent of 500-599µm diameter, was used. SBM were obtained by cutting each suture as small

1 as possible using standard scissors. Technical feasibility and reproducibility of SBM sizing were evaluated on 9
2 different untrained operators.

3 SBM size was measured by automatic microscopic sizer and compared to microspheres (Embozene[®] 900, Boston
4 Scientific, US).

6 **Embolization procedure**

7 Swine renal vascularization anatomy is similar to that of human [14, 15], and the embolization of only one polar
8 artery per kidney remains compatible with life for the 3 months study follow-up. The renal model also allows
9 having both target and control areas in each kidney while comparing SBM and control agent efficacy between the
10 contralateral kidneys. A digital subtraction angiography system (DSA) (Fluorostar, General Electric Medical
11 System, USA) was used for endovascular procedures. Aseptic percutaneous access was performed by femoral
12 arterial puncture with the placement of a 6 French (F) vascular introducer by the Seldinger method [16].
13 Catheterization of arterial vascular targets was performed by an experienced interventional radiologist using a
14 Cobra Wirebraid 5F catheter (Cordis, Fremont, USA). Embolization with SBM was performed in each target artery
15 (left polar kidney artery) after mixing microparticles in a sterile syringe filled with a mix of iodine (Visipaque 320
16 mg I/ml, GE - 30%), physiologic serum (65%) and a small portion of swine blood obtained by reflux through the
17 catheter (5%) to get a better SBM suspension. The right-side embolization was done with Embozene[®] 900.

19 **Technical success and short-term evaluation**

20 The technical success was defined as a complete occlusion of the target artery with no residual flow neither
21 opacification of distal branches in the target territory. The percentage of the embolized area and the non-targeted
22 embolized tissue area were defined after angiographic endpoint as the perfusion defect on DSA control, as a result
23 of subtracting the contoured renal surface with contrast uptake before embolization and after embolization
24 (Horos[™] Software, v3.3.6).

25 Short-term secondary endpoints were safety (non-targeted embolization), ease of use especially the injectability
26 by an evaluation of the embolization procedure time (delay between the first DSA acquisition before the initiation
27 of embolization and the final one confirming technical success).

29 **Medium-term evaluation: clinical criteria, CT and DSA controls, histology study**

30 A three-month follow-up (M3) was chosen (reference standard for animal studies, ISO10993-6) in order to study
31 the medium-term effects of implanted products.

32 During the M3 follow-up, the swine underwent a daily clinical evaluation to look for signs of infection or
33 inflammation (anorexia, signs of malnutrition and abnormal behavior).

34 Contrast enhanced computed tomography scan (CT) were performed on a Discovery CT 750 (GE Healthcare, US)
35 the day before embolization (baseline), at M1 and at M3 after the procedure. Arterial occlusion and possible
36 complications (infiltration of peri-renal fat, abscess, local or distant lymphadenopathy) were evaluated by a trained
37 radiologist on medium-term CT controls, The occurrence of parenchymal atrophy was assessed by measuring
38 cortical thickness and each kidney's volume, estimated by contouring the renal parenchyma on the scan sections
39 performed (IntelliSpace Portal 2015, Philips, Netherlands).

1 DSA controls at M3 assessed the persistence of the arterial occlusion, and the residual kidney perfusion defect as
2 detailed for short-term endpoints.

3 After DSA and CT completion, animals were euthanized, and kidneys were harvested, formalin-fixed and paraffin-
4 embedded. Sections were cut to 4 μ m and stained by hematoxylin-eosin (HE) (AutoStainer, DRS2000 Sakura,
5 Netherlands). The following parameters were evaluated by a trained pathologist blinded to clinical and
6 embolization data : necrosis, fibrin, calcification, cysts, neovascularization, hemorrhage, recanalization, evidence
7 of cellular inflammation [19]. The presence of SBM and Embozene[®] microspheres, and the topography, were
8 evaluated.

10 **Statistical data**

11 SBM parameters data were analyzed by RStudio 1.1463 software (with package ggpubr 0.2.5, programming
12 language R 3.6.1. RStudio Team (2015). RStudio: Integrated Development for R. RStudio, Inc., USA), with
13 evaluation of mean size (with standard deviation (SD). RStudio software was also used for statistics about relative
14 embolized area on DSA and kidneys' volume on CT, with a 95% confidence interval and a Mann-Whitney test for
15 which a p-value $P < 0.05$ was considered significant.

20 **RESULTS**

21 **Suture-Based Microparticles parameters**

22 The average size of SBM prepared from non-absorbable monofilament suture (Flexocrin[®] 2 USP) was 1002 μ m
23 (SD=258). Embozene[®] 900 microspheres have an average size of 877 μ m (SD=25) validating our microscopic
24 measurement method (Figure 1B-1C). The SBM have a rather cylindrical shape since they were cut perpendicular
25 to the long axis of the cylindrical suture when compared to regular Embozene[®] spheres (Figure 1A).

27 **Technical success, feasibility and safety**

28 Technical success as defined was obtained for all SBM and Embozene[®] embolization procedures (Figure 2). The
29 DSA assessment of angiogram defect between the two groups was not statistically different ($P=0.342$): 45.6% on
30 average for SBM group (95% CI [35.9-55.2]) versus 40.5% (95% CI [30.6-55.5]) for Embozene[®] group (Table 1).
31 Three SBM kidneys presented non-targeted embolization, with an average percentage of non-targeted area of 6.5%
32 (4.4-9.3%), versus 2 for Embozene[®] procedure (2.8% (1-4.5%)). SBM injection was significantly slower
33 ($P=0.029$) and less easy than Embozene[®] embolization, respectively 1202s (95% CI [990-1414]) versus 222s (95%
34 CI [194-249]) (Table 1).

36 **Clinical at 3 months**

37 The daily clinical examination follow-up did not show any sign of significant deterioration of general condition,
38 or infection for all animals.

40 **DSA parameters, medium term results**

1 The M3 DSA controls showed a persistent distal perfusion defect with a recanalization with a thin aspect of the
2 target polar artery when compared to the DSA at D0 (Figure 4). The angiogram defect was estimated at 21.9% for
3 the SBM group (95% CI [13.6-30.2]) (Table 2). Comparatively, occlusion by Embozene® particles was also still
4 partially effective with an angiogram defect measured at 25.4%; 95% CI [13.9-36.8]), without significant
5 difference ($P=0.486$). There was no evidence of persistent non-targeted embolization on each kidney at M3 in
6 each group.

8 **CT parameters**

9 CT controls at M1 and M3 showed cortical atrophy corresponding to the embolized area (Figure 3A-3B): the
10 cortical thickness at M3 in these areas was 3mm (1-8mm) for SBM versus 2mm (1-4mm) for Embozene® group
11 (Table 2). Average embolized kidney's volume at M3 were similar in SBM (76.4mL; 95% CI [42.0-110.8]), and
12 Embozene® groups (72mL; 95% CI [59.1-84.8]) ($P=1$) (Figure 3C, Table 2). There was no evidence of
13 complication (abscess, local lymph nodes, peri-renal infiltration, renal excretion failure).

15 **Histology**

16 Macroscopically, SBM (Figure 4A-4B) and Embozene® (Figure 4C) microparticles were visible in the distal
17 embolized area in association with notable cortical atrophy. Histological analysis at M3 showed no significant
18 difference of tissue necrosis or inflammation between the two group (Figure 4D-4E-4F, Table 2). Necrotic
19 rearrangements were found for both groups, associating calcifications, micro-cysts with thin walls, and also non-
20 specific hemorrhagic tissue. The original shape of each embolic agent was preserved at 3 months (Figure 4D-4E-
21 4F).

23 **DISCUSSION**

24 This study aims to implement a new application of the FairEmbo concept by using Suture-Based Microparticles
25 as an available and inexpensive embolic agent, in line with and in addition to a previous study that showed the
26 efficacy and safety of torpedo-shaped suture embolization [7].

27 SBM can be widely available, and as shown, can be easily prepared by different untrained operators. Despite the
28 reproducibility of preparation time and microparticles' size calibration being correct it could have been improved
29 further. In the context of an urgent procedure, the precise calibration of each microparticle seems indeed incidental,
30 with the objective being a simple occlusion of the vessel.

31 The use of nylon-based suture for this preliminary study was adopted because it is used in the manufacture of
32 several prostheses deployed in vascular surgery, and is nowadays incorporated into coils to enhance its
33 thrombogenicity [20, 21]. It can therefore be considered safe considering its bio-toxicity and its degradation in
34 contact with the blood elements.

35 The embolization procedure using SBM is limited by the non-suspension of nylon particles in iodine or saline
36 liquids, which results in an accumulation of microparticles in the bottom of the syringe, and subsequent catheter
37 clogging, particularly at the base of the catheter, similar to previous embolization performed with old fashion PVA
38 microparticles [22]. A small quantity (nearly 5%) of swine blood was needed to increase the surfactant activity of
39 the SBM to prevent catheter clogging. As a result, a longer procedure time was observed for SBM group as

1 compared to Embozene® embolization procedures, probably explained by a smaller quantity of SBM injected per
2 bolus compared to Embozene® spheres injection.

3 *Ex vivo* additional rheological work is underway to improve the injectability of the microparticles, by optimizing
4 the type of suture to improve buoyancy, components of the solution for injection (iodine content, serum content,
5 additive agent increasing the surfactant character such as albumin), syringe and catheter sizer. This will certainly
6 speed up the time required to complete the procedure.

7 The effectiveness of SBM embolization is confirmed by M3 DSA and CTs showing persistent perfusion defect
8 and cortical atrophy in the target areas, without significant evidence of local inflammatory reaction in accordance
9 with the previous FairEmbo report [7]. The risk of local inflammation or infection could vary depending on the
10 different types of sutures and their own inflammatory properties [23-25].

11 The reproducibility of these results in clinical practice needs to be demonstrated. This study was conducted on a
12 swine model because of its anatomical similarities with humans [14, 15] however, swine has different coagulation
13 parameters than humans [26, 27], and these findings may affect the embolization models studied so far.

14 The research on the use of other types of suture could also involve the study of microparticles made from
15 absorbable sutures. The recent development of resorbable microspheres opens the door to new therapeutic
16 approaches for temporary embolization to preserve long term perfusion of the target territory (post-partum
17 bleeding, TACE, bronchial and digestive embolization, retroperitoneal hematoma embolization) [10, 11, 28]. The
18 use of absorbable suture microparticles could then become an available and inexpensive alternative to porcine
19 gelatin sponge, when this is not available, or to new Chitosan microspheres.

21 **CONCLUSION**

22
23 The efficacy and safety of arterial occlusion by SBM could greatly broaden the scope of the FairEmbo concept to
24 include distal embolization with microparticles, in particular for hypervascular lesions as uterine fibroid
25 embolization and hemostatic indications. It allows access to this care in low- and middle-income countries by
26 using suitable embolic material, inexpensive and available worldwide. The FairEmbo technique (suture fragment
27 such as SBM) has a great potential as an embolic agent for emerging countries.

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FIGURE AND TABLE LEGENDS

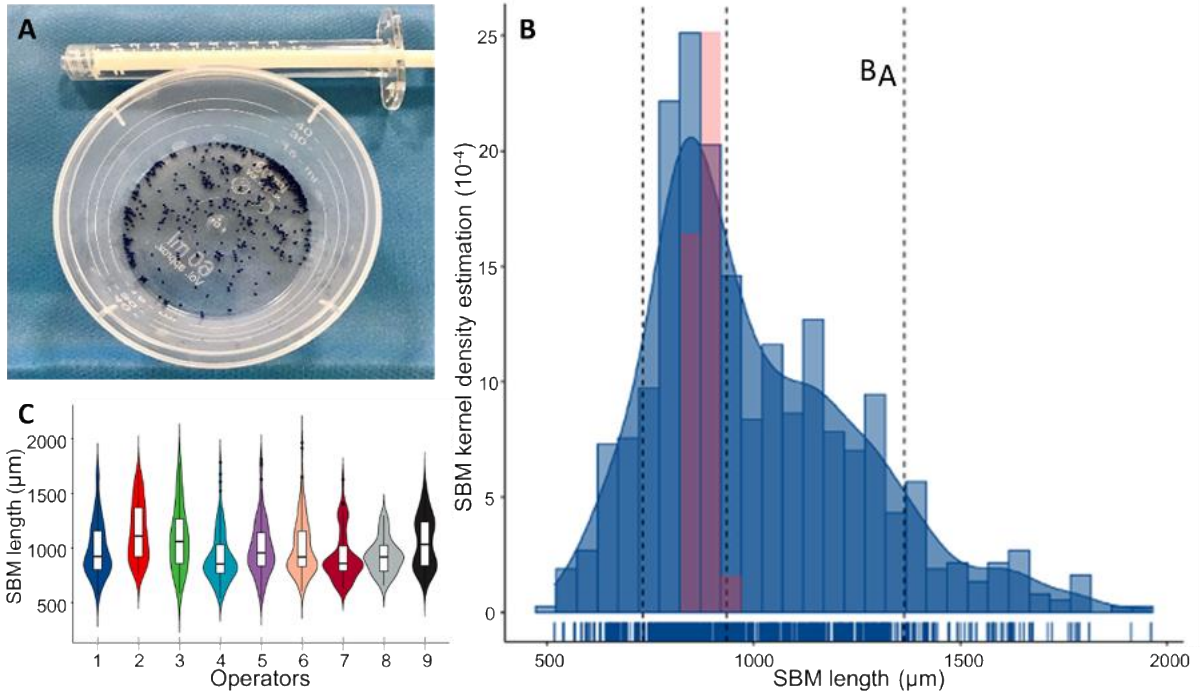
	D0 SBM (n=4)	D0 Embozene® (n=4)	P**
Angiogram defect on DSA control (%) *	45.6 (95% CI [35.9- 55.2])	40.5 (95% CI [30.6- 55.5])	0.342
Non-target embolization (n)	3	2	
Average of non-target embolization area (%)	6.5 (4.4-9.3%)	2.8 (1-4.5%)	0.4
Duration of procedure (s) *	1202 (95% CI [990- 1414])	222 (95% CI [194-249])	0.029

Table 1. Short-term DSA endpoints. *Data shown with 95% confidence interval (95% CI). **Wilcoxon-Mann-Whitney test

	M3 SBM	M3 Embozene®	P**
Angiogram defect on DSA	21.9	25.4	0.486
control (%) *	(95% CI [13.6-30.2])	(95% CI [13.9-36.8])	
Cortical atrophy on CT			
control mm	3 (1-8mm)	2 (1-4mm)	
Volume of kidney on CT	76.1	72.0	1
control (mL) *	(95% CI [42.0-110.8])	(95% CI [59.1-84.8])	
Inflammation parameters			
on CT control †	0	0	
Inflammation parameters			
on histological control ‡	0	0	

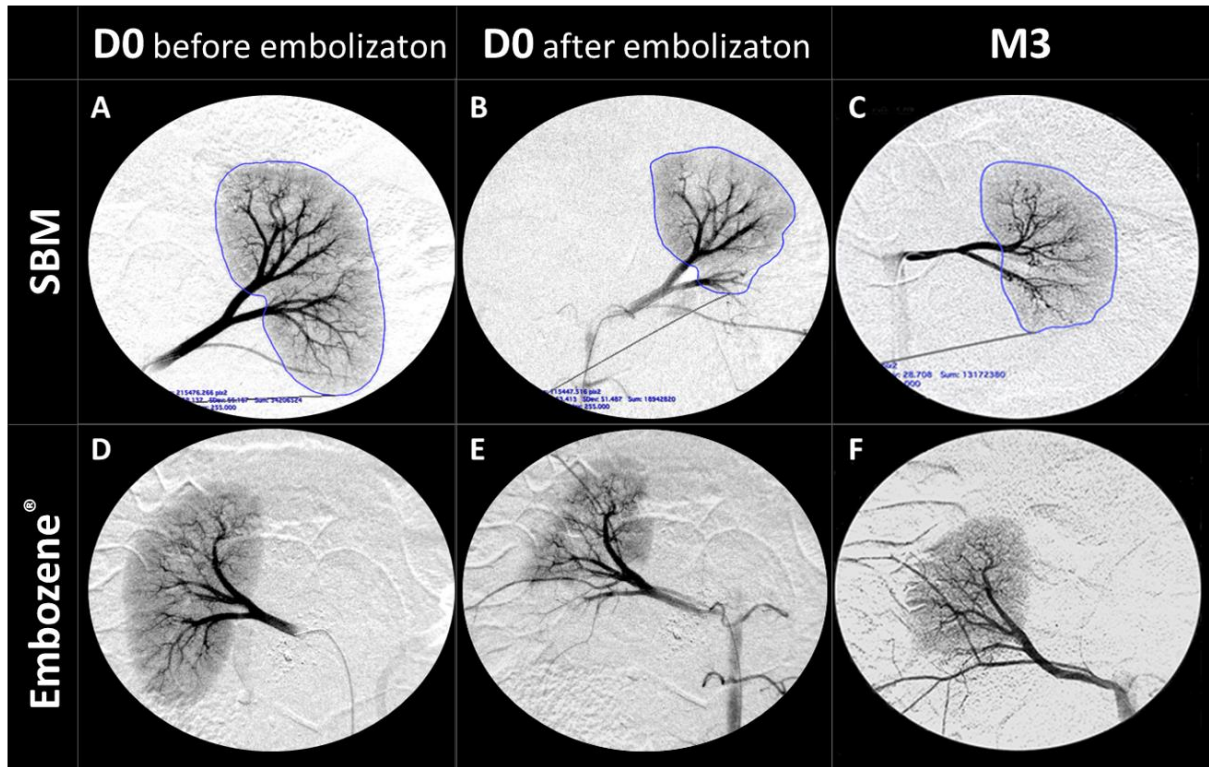
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Table 2. DSA, CT and histological parameters at M3. *Data shown with 95% confidence interval (95% CI). **Wilcoxon-Mann-Whitney test. †peri renal infiltration, abscess, pathological lymph node, urinoma. ‡Abscess, granuloma, significant lymph cell infiltration



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 2 **Figure 1. SBM confection parameters.** (A) Macroscopic aspect of SBM after cutting procedure. (B) SBM length
 3 graphic distribution. Dotted lines represent from left to right respectively the 10th percentile, the median and the
 4 90th percentile. The median size of SBM is 934μm, with an interdecile range from 731 to 1364μm. The red zone
 5 corresponds to the size values of the Embozene[®] microspheres obtained by the same measurement method and
 6 shows that Embozene[®] 900 is a target size for comparison. (C) Reproducibility of SBM confection between each
 7 untrained operator.

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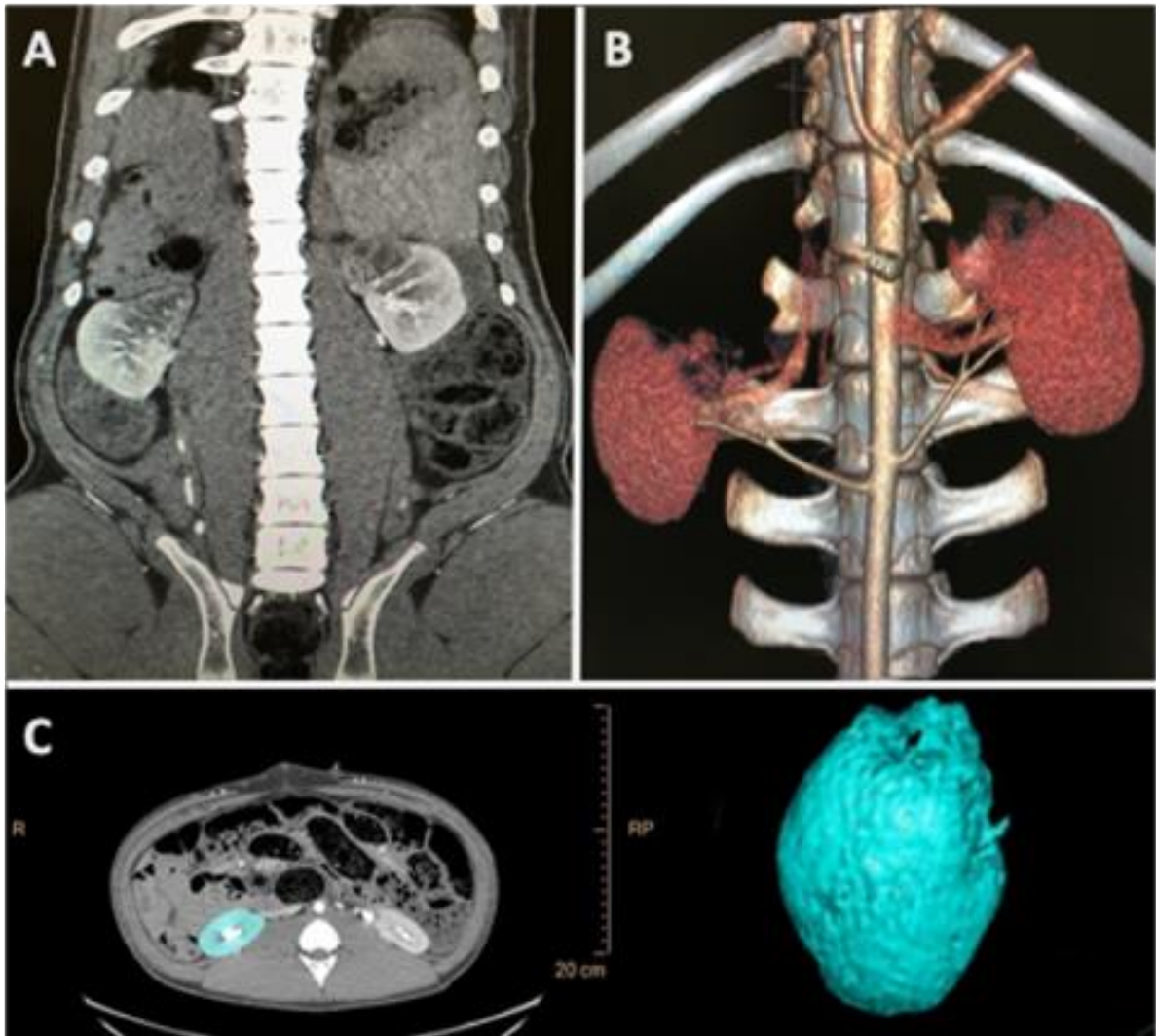


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2 **Figure 2. D0 (before and after embolization) and M3 DSA evaluation.** (A-B-C) SBM embolization DSA
 3 evaluation. DSA controls before (A) and immediately after (B) SBM embolization, and then at M3 (C), with an
 4 example of the analysis of angiogram defect after embolization. In this case, the defect represents 46.6% of the
 5 total angiogram kidney (54.4% of persistent angiogram). DSA controls before (D), immediately after (E) and at
 6 M3 (F) for Embozene® embolization. The same method was used for the perfusion defect evaluation.

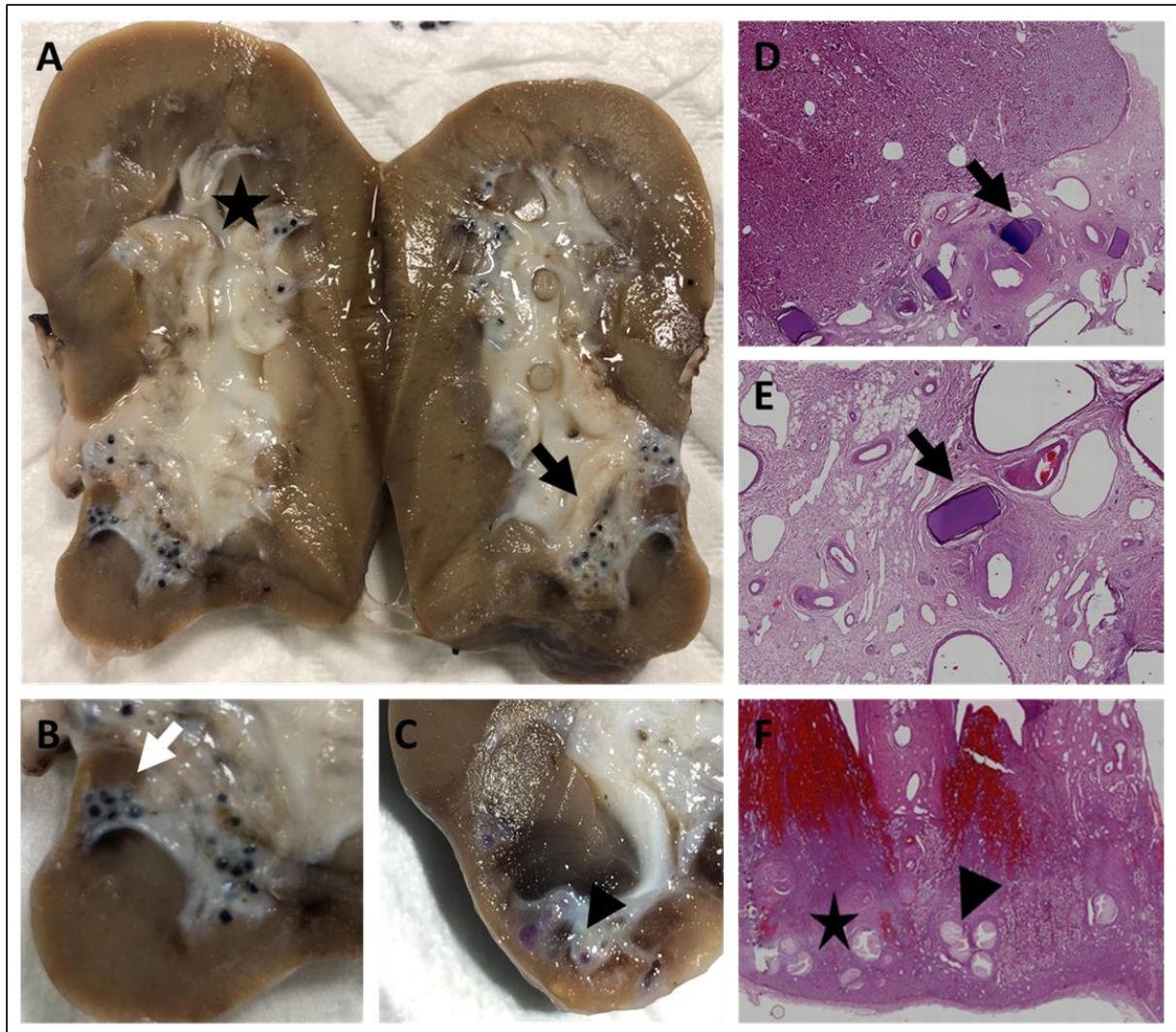
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Figure 3. Three-months CT parameters evaluation. (A) Coronal reconstruction, the upper pole of the right kidney was embolized by Embozene® 900 and the contralateral side was embolized by SBM. There were no sign of complications in particular no inflammatory anomalies such as abscess or local or regional pathological lymph node. (B) Volume Rendering reconstruction showing cortical upper pole defect, suggesting a lack of opacification after embolization. (C) Example of kidney volume measurement based on multi-sections contouring.



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2 **Figure 4. Macroscopic and histological analysis after kidney explantation.** (A) FairEmbo model explant: SBM
3 visible in the distal area of the lower pole (black arrow), with notable cortical atrophy. Note that there are some
4 SBM visible in the upper pole corresponding of non-targeted area (star). (B) FairEmbo model explant showing
5 SBM distal distribution (white arrow). (C) Embozene[®] model explant: microspheres distribution (arrowhead), for
6 comparison. Light microscopy with HE staining (x20) (D), and centered on intra-medullar SBM (x100) (E). SBM
7 are still visible in histological analysis at M3 (arrow). Note the necrosis area (star) around the SBM in comparison
8 to the adjacent healthy parenchyma, suggesting the result of chronic ischemia after effective embolization.
9 Histological analysis with light microscopy of Embozene[®] (arrowhead) embolization, with necrosis area around
10 the spheres (star) (x20) (F).

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