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CLINICAL INVESTIGATION ARTERIAL INTERVENTIONS

Angiographic Detection of Utero-Ovarian Anastomosis and Influence on Ovarian Function After Uterine Artery Embolization

Gabriel T. Sheikh[1] · Arash Najafi[1] · Marc Cunier[1] · Thomas H. Hess[2] · Christoph A. Binkert[1]

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Abstract
Purpose To assess the detectability and frequency of the different types of utero-ovarian anastomosis, the correlation between type of anastomosis and ovarian failure after UAE, as well as the impact of coiling as a strategy for the prevention of ovarian failure.
Materials and Methods We retrospectively studied a population of 92 women treated with uterine artery embolization at our institution between 2007 and 2017. Utero-ovarian anastomoses were categorized on angiographic sequences by two radiologists based on the classification published by Razavi et al. (Radiology 224(3):707–712, 2002), and Cohen's kappa was calculated. Ovarian failure was defined as an increase in serum FSH above 27 mIU/ml three months after embolization.
Results Out of a total of 184 anastomoses, 27% were classified as type Ia, 45% as type Ib, 1% as type II and 24% as type III. Three percent of anastomoses could not be determined. There was very good inter-observer reliability on the classification of utero-ovarian anastomoses ($\kappa = 0.847$). Ovarian failure occurred in six out of 92 women (7%). Each had at least one type Ib ($n = 4$) or type III ($n = 1$) anastomosis, with the exception of one patient in whom the type of anastomosis could not be determined. All women presenting with ovarian failure were 45 years of age or older. No patient with protective coiling developed ovarian failure.
Conclusion Utero-ovarian anastomoses are more common than previously expected and can be reliably classified with very good inter-observer reliability. Patients with type Ib and type III anastomoses carry the risk of ovarian failure after uterine artery embolization. Protective coiling seems to be an adequate strategy for avoiding ovarian failure in those types of anastomoses.

Keywords Uterine artery embolization · Utero-ovarian anastomoses · Arterial angiography · Ovarian function · Protective coiling

Abbreviations

UAE	Uterine artery embolization
UOA	Utero-ovarian anastomosis
FSH	Follicle-stimulating hormone
MRI	Magnetic resonance imaging
SD	Standard deviation

✉ Gabriel T. Sheikh
gabriel.sheikh@ksw.ch; gabrielsheikh@yahoo.de

[1] Department of Radiology and Nuclear Medicine, Cantonal Hospital Winterthur, Brauerstr. 15, 8401 Winterthur, Switzerland

[2] Department of Obstetrics and Gynecology, Cantonal Hospital Winterthur, Brauerstr. 15, 8401 Winterthur, Switzerland

Introduction

Uterine leiomyomas are the most common benign gynecologic neoplasms in women of childbearing age [1, 2]. They can become clinically apparent, mainly through abnormal uterine bleeding and/or bulk symptoms. A safe and effective treatment for symptomatic uterine leiomyomas, which has been well established, is uterine artery embolization [3]. Two areas of concern that remain with uterine artery embolization are the risk of ovarian failure and insufficient infarction of the targeted uterine leiomyomas, which have been postulated to depend on the type of anastomosis between the uterine artery and the ovarian artery [4, 5].

A classification developed by Razavi et al. [6] describes three different types of utero-ovarian anastomoses. In type I anastomoses, blood flow is directed toward the uterus, while in type III anastomoses blood flow is directed toward the ovary (Fig. 1). In type II “anastomoses,” there is no connection between the ovarian and the uterine artery, with parts of the uterus or fibroids being supplied solely by the ovarian artery, apparent by incomplete depiction of the uterus' vascular bed on bilateral uterine artery angiograms. Type I anastomoses are further divided into type Ia with blood flow directed from the ovarian artery into the uterus' vascular bed without contrast reflux during power injection (Fig. 2) and type Ib anastomoses which are temporarily contrasted during injection into the uterine artery, due to weaker flow, and subsequently washed out (Fig. 3). While type Ib and type III anastomoses can increase the risk of ovarian failure due to the possibility of embolization particles reaching the ovarian capillaries [4, 5, 7, 8], type Ia and type II anastomoses have been associated with the risk of insufficient infarction of the targeted uterine leiomyomas [9, 10], as target vessels might not be reached by the injected particles.

This emphasizes the importance of determining the type of anastomosis by carefully looking at the uterine artery angiogram before uterine artery embolization in order to enable the interventional radiologist to adapt the embolization strategy for an optimal outcome. Despite the potential impact on the outcome of uterine artery embolization, utero-ovarian anastomoses are still not widely classified in clinical practice. Our study aims to assess detectability of the type of utero-ovarian anastomosis based on the classification developed by Razavi, as well as the impact of coiling as a strategy for the prevention of ovarian failure.

Materials and Methods

After obtaining approval for our retrospective study from the local ethics committee, we conducted a database search for patients treated with uterine artery embolization at our institute between 2007 and 2017. All patients were treated by the same experienced interventional radiologist to ensure the consistency of the embolization technique. In total, $n = 277$ women were treated with bilateral uterine artery embolization during the above-mentioned period, out of whom $n = 92$ had the dataset of FSH serum levels available before and three months after the embolization, required for inclusion into our study.

Patient age at UAE was documented. The mean age of our population was 42 years (SD $\pm$ 6 years, range 26–57 years) (Table 2). The indication for uterine artery embolization was recorded as bulk symptoms, abnormal uterine bleeding or both. The clinical outcome was

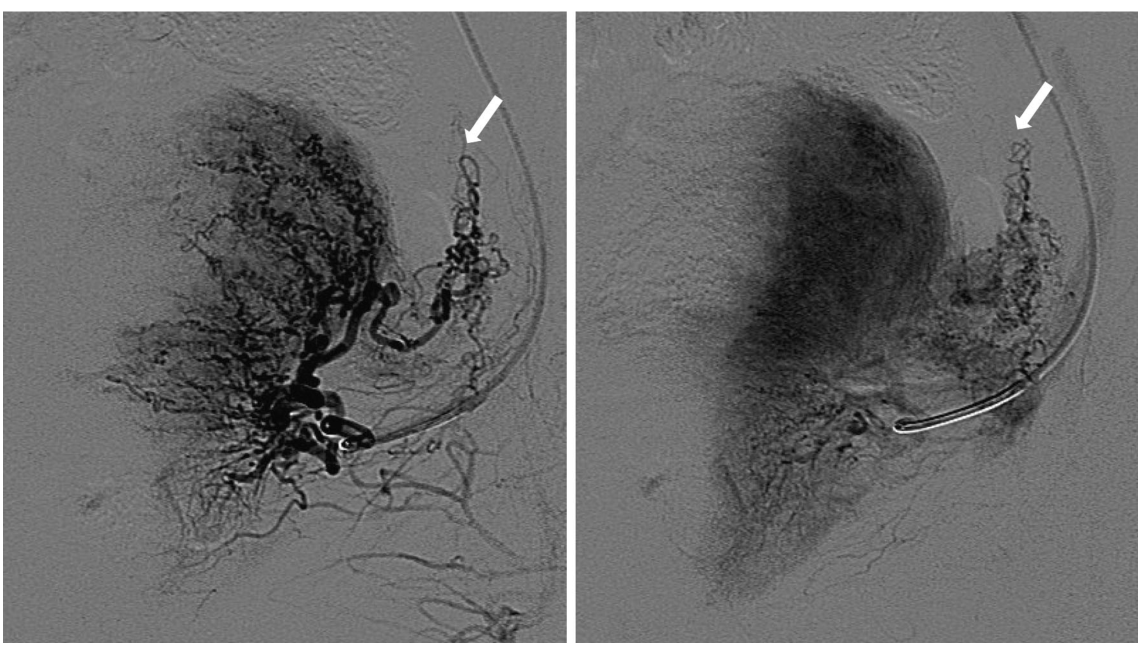

Fig. 1 Angiogram of the left uterine artery with type III anastomosis 3 s (left) and 5 s (right) after contrast injection. Contrast in utero-ovarian anastomosis and ovarian vascular bed during contrast injection. No retrograde washout

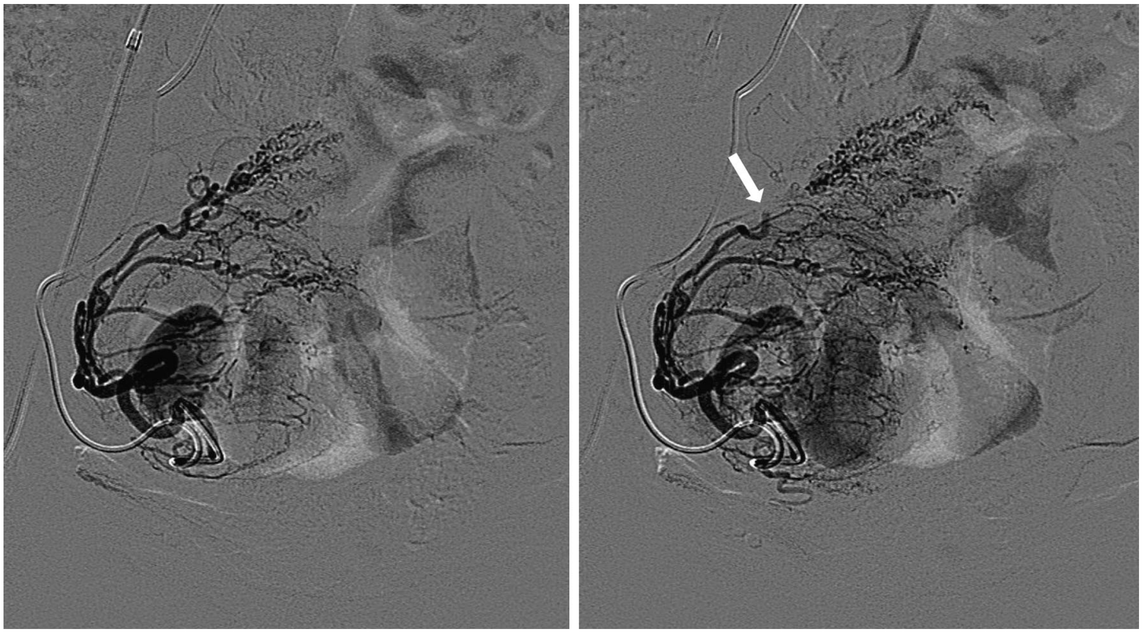

Fig. 2 Angiogram of the right uterine artery with type Ia anastomosis 2 s (left) and 3 s (right) after contrast injection. Utero-ovarian artery not contrasted during contrast injection. Washout of branch of uterine artery after contrast injection (white arrow)

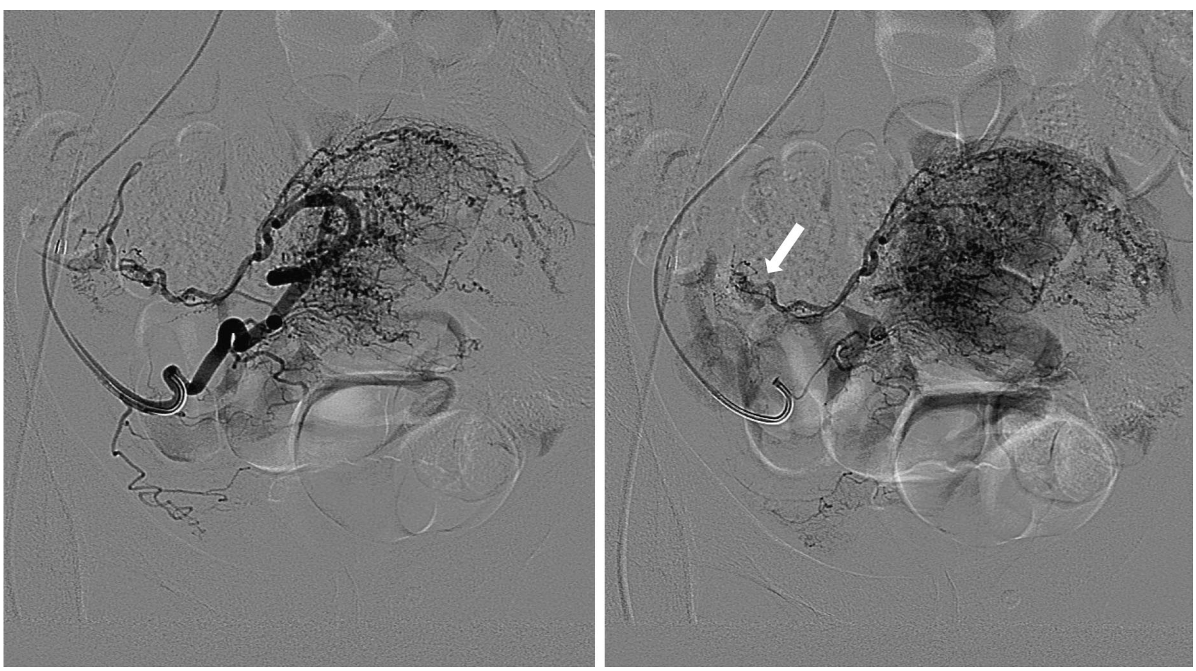

Fig. 3 Angiogram of the right uterine artery with type Ib anastomosis 3 s (left) and 5 s (right) after contrast injection. Contrast in utero-ovarian anastomosis during contrast injection with retrograde washout after contrast injection (white arrow)

investigated, looking for an improvement in clinically apparent symptoms post-treatment. FSH serum levels were examined for an increase above the threshold of 27 mIU/ml, which is the cutoff at our laboratory for menopause. An increase of at least 20 mIU/ml was used as an additional criterion to increase the sensitivity of serum FSH as a marker for ovarian failure.

All of our patients underwent MRI of the pelvis, including MR angiography before uterine artery embolization. Following selective catheterization of the uterine artery with a 4F catheter, an angiogram of the uterine artery was created in a standardized way by power injection of diluted contrast agent (2:1, Ultravist 370, Bayer AG, Zurich, Switzerland). The flow rate was adjusted for each uterine artery, depending on the result of a manual test injection performed beforehand. A flow of 2 ml/s for 2 s was chosen for standard uterine arteries, while flow was adjusted to 3 ml/s for 2 s in case of larger uterine arteries.

In cases of utero-ovarian anastomoses with intra-interventionally apparent utero-fugal (type III) or very weak utero-petal (type Ib) flow within the utero-ovarian anastomosis, protective coiling of the artery was our first-line approach to protect the ovaries from collateral embolization. In cases where coiling seemed not feasible, e.g., due to tortuous uterine artery branches, the size of the trisacryl gelatine embolization particles (Embosphere, Merit Medical, South Jordan, USA), used for embolization, was increased from the usual 500–700 μm to 700–900 μm in order to minimize the risk of unwanted embolization of the ovary and to avoid the increased radiation exposure accompanied with the attempt to coil under difficult conditions.

The endpoint used for uterine artery embolization was distal filling of the uterine artery branches with embolization beads, depicted as small defects within those vessels, resembling a cobble stone pattern on digital subtraction angiography.

Angiograms of the uterine arteries were retrospectively evaluated as follows. Ten test cases not included in our cohort were discussed beforehand to reach an agreement on the interpretation and definition of the different types of utero-ovarian anastomoses. Based on the classification described by Razavi et al., angiograms were independently assessed for presence and type of utero-ovarian anastomosis through careful observation by two blinded radiologists not involved in the UAE procedure (Table 1). In cases of disagreement, the definite type of anastomosis was determined by a senior interventional radiologist.

Cohen's kappa was calculated for the inter-rater agreement on the presence and the classification of utero-ovarian anastomoses, and mean comparison was performed for the age of coiled patients versus patients without coiling using SPSS (IBM SPSS Statistics V25, Armonk, NY, USA).

Results

Sixty-one percent of those women complained about heavy menstrual bleeding ($n = 56$), 15% of women experienced bulk symptoms ($n = 14$), and 24% of women had bulk symptoms as well as heavy menstrual bleeding ($n = 22$) before uterine artery embolization. Three months post-embolization, 87 women reported an improvement in the above-mentioned symptoms, while five women were not satisfied with the post-treatment results due to persisting symptoms (Table 2).

Utero-ovarian anastomoses could be detected in 178 out of a total of 184 uterine arteries. Twenty-seven percent of anastomoses were classified as type Ia ($n = 49$), 45% as type Ib ($n = 83$), 1% as type II ($n = 2$) and 24% as type III ($n = 44$). We did not find any anastomosis in 3% of cases ($n = 6$) (Table 2). Cohen's kappa for presence of an anastomosis showed moderate inter-rater agreement ($\kappa = 0.558$). There was disagreement about the type of anastomosis in 17 out of 184 cases, which results in a very good inter-rater reliability ($\kappa = 0.847$), based on the interpretation of the kappa value as described by Landis and Koch in 1977 [11].

In most of our patients, bilateral anastomoses could be detected ($n = 87$), with symmetric anastomoses in $n = 40$ women ($n = 11$: Ia, $n = 23$: Ib and $n = 6$: III) and asymmetric anastomoses in $n = 47$ women. In $n = 4$ patients, an anastomosis could only be found unilaterally, and in one patient, no anastomosis was found on either side.

Seven percent of women ($n = 6$) showed an increase in serum FSH levels above the threshold of 27 mIU/ml with an increase of at least 20mIU/ml three months after uterine artery embolization (Table 3). Sixty-seven percent ($n = 4$) of patients with ovarian failure had a minimum of one type Ib anastomosis, while 17% ($n = 1$) had at least one type III anastomosis. In one of the patients, an anastomosis could not be outlined on one side. All women exhibiting ovarian failure were 45 years of age or older.

Table 1 Modified from Razavi et al. [6]

	Rules to determine type of utero-ovarian anastomosis
Ia	No contrast in utero-ovarian anastomosis during contrast power injection. Wash-in of non-contrasted blood into vascular bed of uterine artery after contrast injection
Ib	Contrast in utero-ovarian anastomosis ± ovarian vascular bed/ovarian artery during contrast power injection, but retrograde washout of contrast in utero-ovarian anastomosis after contrast injection
II	Incomplete contrasting of uterine vascular bed after contrast power injection into both uterine arteries
III	Contrasting of utero-ovarian anastomosis and ovarian vascular bed ± ovarian artery during contrast power injection and persistence of contrast agent after contrast injection

Table 2 Patient population

Sample size	92
Age	
Mean	41.53
Standard error	0.65
Median	42.5
Mode	45
Standard deviation	6.22
Sample variance	38.71
Range	31
Minimum	26
Maximum	57
Symptoms	
Bulk symptoms	14
Abnormal bleeding	56
Both	22
Symptom improvement	
Yes	87
No	5
Suspected ovarian failure	
Yes	6
No	86
Anastomoses	
Type Ia	49
Type Ib	83
Type II	2
Type III	44
No anastomosis	6

Table 3 FSH in women with suspected ovarian failure [mIU/ml]

Patient no	Before UAE	3 months post-UAE
1	2	32
2	11	32
3	15	56
4	2.6	29
5	5.8	40
6	7.2	32

UAE uterine artery embolization, *FSH* follicle-stimulating hormone

A total of 21 anastomoses, all type Ib and type III, were coiled for protection of the ovary. No patient with protective coiling developed ovarian failure.

The age of the subgroup of patients that were coiled was 39 years on average with a minimum of 28 years and a maximum of 53 years compared to a mean of 42.24 years in the population without coiling with a minimum of 26 years and a maximum of 57 years. The Welch test as well as the *T* test for unequal variances showed no statistically significant difference between both subgroups ($p = 0.072$).

Discussion

While previous studies reported the incidence of utero-ovarian anastomoses to be between 32 and 35% [6, 8], we found anastomoses to be detectable much more frequently. The very good inter-rater reliability in respect of the type of utero-ovarian anastomosis shows that a high rate of detection and agreement is possible through careful evaluation of direct contrasting of an utero-ovarian anastomosis as a direct sign or wash-in of non-opacified blood into the vascular bed of the uterine artery as an indirect sign.

Razavi et al. reported 13% and Lanciego et al. only 7% of type Ia anastomoses in their cohorts. This could, in part, be due to the very subtle inflow of non-contrasted blood from the ovarian artery into the vascular bed of the uterus occurring in some cases.

While type Ib anastomoses were the most common type in our study, they were only reported in 9% of arteries in the study by Razavi et al. and 6% of cases in the study by Lanciego et al. In the case of a low backflow, this type of anastomosis can easily be mistaken for type III anastomosis. It is therefore necessary to carefully observe backflow within the utero-ovarian artery across the entire time frame. The distinction between type Ia and type Ib anastomoses may also be subject to variability, since retrograde flow of contrast material into the anastomosis positively correlates with the amount of contrast agent injected as well as the injection pressure used [12].

An embolization-induced increase in pressure within the capillary bed of the uterus can change hemodynamics toward utero-fugal blood flow, especially when blood flow in type Ib anastomoses is low [13]. It might therefore be useful to further characterize this type of anastomosis as high flow and low flow.

Type II anastomoses can only be detected indirectly on uterine artery angiograms; it is possible that some of the patients without detectable utero-ovarian anastomoses could, in fact, have type II anastomoses.

Lanciego et al. reported type III anastomoses in 22% of cases matching our results. In contrast, Razavi et al. reported type III anastomoses in only 7%. Identifying this type of anastomosis is crucial since type III anastomoses have been particularly associated with the risk of ovarian failure. Type III anastomoses which were projected onto the uterus were especially difficult to detect. Identifying the location of the ovaries on pre-interventional MRI might help to improve the detection rate of this type of anastomosis.

Our results at 3 months match those from The Fibroid Registry which reports 95% of patients as having improved symptoms at 12 months following UAE [14], thus confirming the effectiveness of UAE for the treatment of symptomatic uterine fibroids.

We determined ovarian failure by measuring serum FSH levels, a well-established [15–18] and more objective parameter for menopausal transition than amenorrhea. An increase in FSH levels during menopausal transition has been confirmed in large epidemiologic cohorts [17, 18] and occurs due to follicle depletion with consecutive relative loss of inhibins [15].

All but one of the women with an increase in FSH after UAE had at least one detectable type Ib or III anastomosis. The exception was a patient in whose angiogram only a left-sided type Ia anastomosis could be identified. Since antegrade flow in type Ia anastomoses protects the ovary against inflow of infarcting embolization beads, it is reasonable to assume that this patient might have had an undetected right-sided type Ib or III anastomosis. This assumption is also supported by the fact that none of the women with a significant increase in serum FSH had bilateral type Ia anastomoses.

Age has been demonstrated to be a main risk factor for ovarian failure after UAE, with women over the age of 45 years being at a much greater risk than women under the age of 45 years [8, 14, 19–21]. This may be explained by a greater ovarian reserve in younger women, who seem to have a greater capacity for recovery after ovarian damage [22]. Nevertheless, the ovarian reserve may still be decreased after UAE in this population [23]. Resilience against ovarian failure is negatively correlated with age, but age is not an absolute predictor. Even though all of the patients in our study who developed ovarian failure were 45 years of age or older, ovarian failure can also occur in patients under the age of 45 years [8, 14, 19–21], making this cutoff a rather arbitrary one.

Our data support the effectiveness of coiling as protection against ovarian failure in low-flow type Ib as well as type III anastomoses. In cases in which coiling is not possible, e.g., due to tortuous anastomoses, we use larger beads to minimize the ischemic potential. This strategy is backed by the high clinical success rates after UAE, as well as the low total of ovarian failures in our study.

The limitations of our study are the retrospective design as well as the relatively low number of patients in our study population. The use of FSH as marker for ovarian failure is another limitation owed to the retrospective design of our study, as more recent studies have suggested anti-Mullerian hormone to be a more accurate single marker for ovarian function [22, 24].

Conclusion

Through careful observation of direct and indirect signs, utero-ovarian anastomoses can be found in the majority of uterine artery angiograms with a very good inter-rater reliability for the type of anastomosis.

While not only type III, but also type Ib anastomoses carry an increased risk of ovarian failure after UAE, the overall risk is low, especially for women under the age of 45 years.

This risk can be further minimized by deploying adequate strategies for protecting the ovaries, such as protective coiling, in cases where a type Ib or type III anastomosis is detected.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in our study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent This study has obtained IRB approval from the Cantonal Ethics Committee Zurich, and the need for informed consent was waived.

Consent for Publication For this type of study, consent for publication is not required.

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