Foam Sclerotherapy for Cyst Volume Reduction in Autosomal Dominant Polycystic Kidney Disease: A Prospective Cohort Study

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Rationale & Objective: Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disorder. Progressive increase in cyst number and size leads to kidney failure in a majority of patients. Large kidney cysts, although few, can be especially deleterious by impeding kidney blood flow and obstructing urine flow over a large region. Foam sclerotherapy is a minimally invasive procedure that may be used to ablate large cysts. We examined the effectiveness and safety of foam sclerotherapy for kidney volume reduction in patients with ADPKD.

Study Design: Prospective cohort study.

Setting & Participants: Adults with ADPKD at a tertiary referral center in Toronto.

Predictor: Foam sclerotherapy.

Outcomes: Volume of treated kidneys and adverse events.

Analytical Approach: Treated and nontreated kidney volume, kidney function, tolerability, and symptoms were analyzed within each patient.

Results: We performed 77 foam sclerotherapy treatment sessions in 66 patients. Foam sclerotherapy was associated with a 21.8% volume reduction of the treated kidneys (n = 95; median, 1,138 [IQR, 801-1,582] mL before vs 891 [IQR, 548-1,450] mL after; P < 0.001), while the volume of the nontreated kidneys increased by 3.4% during the same time frame (n = 37; median, 655 [IQR, 352-998] mL before vs 677 [IQR, 371-1,164] mL after; P < 0.001). 4 (6%) patients had a higher measured creatinine clearance by at least 10 mL/min at least 12 months after foam sclerotherapy. 9 (14%) patients experienced self-limiting pain at the procedure site and 2 (3%) had cyst or urinary tract infection. Most patients with flank/back pain, abdominal pain, and abdominal distension had improvement in their symptoms.

Limitations: Small sample, observational data.

Conclusions: Foam sclerotherapy is a safe and effective procedure for kidney volume reduction and amelioration of compressive symptoms in select patients with ADPKD. Further studies are needed to assess its effects on kidney blood flow and kidney function and determine the subgroups of patients most likely to benefit.

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disorder worldwide, with a lifetime risk of 1:1,000.1 Overall, ADPKD accounts for 5% to 8% of all cases of end-stage kidney disease in developed countries.2 Progressive cyst expansion leads to distortion of kidney architecture and ultimately end-stage kidney disease in a majority of patients. Although kidney function typically remains stable during the first 3 to 4 decades of life, kidney volume expands quasi-exponentially during adult life on average at ~5% per year.3,4 Total kidney volume is a strong predictor for the subsequent decline in glomerular filtration rate (GFR), with patients having a total kidney volume > 1,500 mL at high risk for developing end-stage kidney disease.5 As total kidney volume expands, kidney blood flow declines inversely even when GFR remains normal or near normal and is a strong predictor for progression in ADPKD.5,6 Large cysts (≥5 cm in diameter), though few in number, can be especially deleterious by impeding blood and obstructing urine flow in many nephrons over a large region.7 Tolvaptan is currently the only treatment approved for ADPKD to slow the rate of total kidney volume expansion in high-risk patients.8,9 However, tolvaptan does not reverse total kidney volume expansion; there is presently no effective therapy to reduce kidney volume in ADPKD.

Imaging-guided percutaneous cyst aspiration has been used for treatment of simple kidney cysts for the past 4 decades and is considered safe and minimally invasive.10 Because simple cyst drainage without sclerotherapy is associated with a high recurrence rate (30%-80%), attempts have been made to destroy the secretory epithelium by intracystic injection of sclerosing agents, such as ethanol.11 Sodium tetradecyl sulfate is a sclerosing agent that has been safely used for many years for treatment of varicose veins, epidydimal cysts, and hydroceles.12,13 It has also been compared with ethanol for ablation of simple kidney cysts, with similar success rates but less frequent pain.14 We have used sodium tetradecyl sulfate foam sclerotherapy15 for treatment of large symptomatic (≥5 cm in diameter) liver and kidney cysts in ADPKD. In this feasibility study, we examined the efficacy and safety of...
sodium tetradecyl sulfate foam sclerotherapy for experimental kidney volume reduction in ADPKD.

**METHODS**

All patients were recruited from the Hereditary Kidney Disease Clinic at the Toronto General Hospital, a speciality clinic that follows up more than 500 patients with ADPKD from the Greater Toronto Area with a population of approximately 6 million. All patients were assessed by interventional radiology before treatment, all gave consent, and the study protocol was approved by the local Research Ethics Board (approval number: 16-5818-BE).

Foam sclerotherapy was performed by an interventional radiologist under sterile conditions using local anesthetic and intravenous sedation. Target ablation of large (≥5 cm) kidney cysts (generally up to 2 cysts per session) was performed under real-time ultrasound guidance. After insertion of a 6 Fr (2 mm) drainage catheter using a trocar or Seldinger approach, contrast was injected to fluoroscopically confirm the drain position and the absence of contrast leakage outside the cyst. The target cyst was then drained completely before instilling the sodium tetradecyl sulfate, and the volume removed was recorded.

We used 3% sodium tetradecyl sulfate, an anionic detergent approved by both Health Canada and the US Food and Drug Administration, as the sclerosant. Although the maximum sodium tetradecyl sulfate dose for intracystic injection is not well defined, we conservatively used the maximal dose approved by the US Food and Drug Administration for a single intravenous treatment of varicose veins (10 mL). This dose was believed to be safe because the majority of the sodium tetradecyl sulfate is not absorbed and is ultimately aspirated from the cyst at the end of the procedure. Sodium tetradecyl sulfate was mixed with room air to form a foam and instilled into the targeted cyst. The maximal dilution ratio was 1 mL of sodium tetradecyl sulfate for 10 mL of air, although the ratio varied depending on cyst volume. Moderately large (5-7 cm) cysts were targeted in a single session, while very large (>7 cm) cysts were treated in 2 sessions 1 week apart. For cysts >10 cm, only 1 cyst was ablated at a time. Up to 40% of the cyst volume removed was replaced with sodium tetradecyl sulfate foam; however, no sodium tetradecyl sulfate was instilled in the case of bloody cyst fluid or suspicion that the target cyst cavity was not intact. If more than 1 cyst was drained, the amount of sclerosant to be injected was allocated between the cysts according to cyst volume.

After instillation of the foam, the drains were subsequently capped and the patient was returned to the recovery room to perform 90° rotations of their body while lying supine every 15 minutes for 1 hour; this ensured optimal sodium tetradecyl sulfate coating of the cyst interior. The bags were subsequently opened for free drainage for 30 minutes, followed by aspiration of any remaining sodium tetradecyl sulfate. For single-session treatment, the drain was removed at this point. For patients undergoing 2-session treatment, the patient was discharged with the drain open to a bag. The patient returned 1 week later for another sodium tetradecyl sulfate injection before final removal of the drain.

Heart rate and blood pressure were monitored in patients during and after foam sclerotherapy. All adverse events were recorded in the procedural report. Serum creatinine level and measured 24-hour creatinine clearance were assessed before and after each intervention. Patients underwent follow-up kidney function measurement with a 24-hour urine collection at 1 to 3 months, 4 to 6 months, and 12 months or more after foam sclerotherapy. Creatinine clearance was corrected for baseline urinary creatinine excretion rate.

Magnetic resonance imaging (MRI) was performed in all study patients before sclerotherapy. Postprocedure imaging

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**Figure 1. Study flowchart.** Sixty-eight consecutive patients were scheduled for foam sclerotherapy but 66 were treated and analyzed. Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; AKI, acute kidney injury.
was performed at least 3 months after foam sclerotherapy, based on evidence that maximal volume reduction with the use of sclerosant occurs within 3 to 12 months after cyst ablation.15-17 Most patients underwent a standardized MRI protocol as previously described in the Toronto Genetic Epidemiology Study of Polycystic Kidney Disease (TGESP), while a few with severe claustrophobia underwent computed tomography instead.18 Kidney volume was computed by 2 experienced radiologists (M.P. and S.F.S.) with a segmentation method using manual contouring in Vitrea (Vital Images; Toshiba Medical Systems) and Aquarius Intuition (TeraRecon) on 4- to 6-mm coronal T2-weighted magnetic resonance half-fourier acquisition single-shot turbo spin echo images with fat suppression (GE 1.5-T Signa HDXT; GE Healthcare).19 Patients were asked to complete a scale-based questionnaire to quantify change in mass effect–related symptoms postprocedure.

Categorical and continuous variables were reported as percentage and mean ± standard deviation, respectively; kidney volume measurements were reported as median (interquartile range [IQR]) because they were not normally distributed. Patient characteristics of the Toronto Genetic Epidemiology Study of PKD (TGESP) cohort were compared using t test, Mann-Whitney test, Fisher exact test, and χ² test. Outcome variables were assessed in patients before and after each procedure using paired t test or Wilcoxon signed rank test for non-normally distributed variables. Differences in the change in kidney volume were compared between targeted and nontargeted kidneys using Mann-Whitney test. Analyses were performed using GraphPad Prism 5.0.0 and Excel (Microsoft Office 2013).

RESULTS

Characteristics of Study Patients

The study flow chart is shown in Figure 1. Between November 1, 2014, and August 30, 2017, we performed foam sclerotherapy in 68 consecutive patients with 1 or more large nonexophytic kidney cyst (>5 cm in its greatest dimension). Two patients were excluded from the analysis: 1 developed contrast nephropathy during investigation for cyst hemorrhage before his scheduled foam sclerotherapy and another did not undergo foam sclerotherapy because of rupture of his target cyst. Foam sclerotherapy was performed in 41 (62%) patients with “mass effect” symptoms due to enlargement of their cystic kidneys and as an experimental procedure in the remaining patients for potential improvement in blood pressure and kidney function.

Clinical characteristics of the study cohort are shown in Table 1. Mean age was 52 years and 55% of participants were women. Baseline mean serum creatinine level and creatinine clearance were 1.1 mg/dL and 85.4 mL/min, respectively. Twelve (18%) patients had a baseline creatinine clearance < 60 mL/min. Baseline total kidney volume was 1,920 (IQR, 1,380–3,160) mL. Nearly 40% of patients had PKD2 mutations, followed by no mutation detected (23%), PKD1 protein-truncating (21.2%), and PKD1 missense (13.6%) mutations.

Effectiveness of Cystic Kidney Volume Reduction

Table 2 summarizes technical characteristics of 77 foam sclerotherapy treatment sessions in 66 patients. Most patients were treated unilaterally (39% in the left kidney only and 35% in the right kidney only). Mean interval of kidney volume measurements by MRI pre- and post–foam sclerotherapy was 13.6 ± 4.9 months (when a patient had >1 foam sclerotherapy session, the most recent MRI was used). In total, 95 kidneys were treated and 37 were not.

We found that foam sclerotherapy significantly reduced the volume of the targeted kidneys by 21.8% (n = 95 kidneys; median, 1,138 [IQR, 801–1,582] mL before vs 891 [IQR, 548–1,450] mL after; P < 0.001), while the volume of the nontargeted kidneys increased by 3.4% (n = 37 kidneys; median, 655 [IQR, 352–998] mL before vs 677 [IQR, 371–1,164] mL after; P < 0.001; Fig 2). Overall, 38 of 66 (57.6%) and 18 of 66 (27.3%) patients experienced >20% and between 10% and 20% of volume reduction of their targeted kidney at least 3 months after the procedure. Visual inspection of the targeted kidney cysts showed no change in size up to 12 months postprocedure.

Table 1. Clinical Characteristics of Study Cohort

| Characteristic                  | n = 66 |
|--------------------------------|--------|
| Age, y                         | 52.0 ± 13.0 |
| Sex, Men                       | 30 (45.5%) |
| Baseline Scr, mg/dL            | 1.1 [0.8-1.4] |
| Baseline CLcr, mL/min          | 84.0 ± 39.0 |
| Baseline total kidney volume, mL| 1,920 [1,380-3,160] |
| Mutation class                  |         |
| PKD1 protein-truncating        | 14 (21.2%) |
| PKD1 non-truncating            | 9 (13.6%) |
| PKD2                            | 27 (40.9%) |
| No mutation detected           | 15 (22.7%) |
| Mosaic (PKD1 protein-truncating)| 1 (1.5%) |

Table 2. Technical Characteristics of Sclerotherapy Treatment Sessions

| Characteristic                  | n = 77 |
|--------------------------------|--------|
| Sclerotherapy site              |        |
| Left kidney only                | 30 (39.0%) |
| Right kidney only               | 27 (35.0%) |
| Both kidneys                    | 20 (26.0%) |
| Patients treated >1×            | 11 (14.3%) |
| Single vs 2 sessions            |        |
| Single                          | 28 (36.4%) |
| ≥2 sessions                     | 49 (63.6%) |

Note: Data are expressed as number (percent).
These data suggest permanent ablation of the targeted cysts in a majority of patients.

Safety and Adverse Events

No patient experienced any significant change in blood pressure or hemodynamic instability during or after foam sclerotherapy. Nine (13.6%) patients experienced pain after foam sclerotherapy: 5 required analgesia; in 2, the pain lasted for at least 1 month. Three potential episodes of infection were documented: 1 patient developed low-grade fever and sore throat 5 days after foam sclerotherapy and was treated by her family physician with oral cefixime for 4 days empirically for suspected cyst infection. Her antibiotic treatment was withheld and she underwent diagnostic aspiration of a complex cyst that revealed negative cultures. In addition, her urine and blood cultures were negative. Her fever resolved without further intervention. Two other patients were diagnosed to have definite foam sclerotherapy–associated pyelonephritis or infected cyst based on clinical findings and positive blood or cyst fluid cultures. One patient reported asymptomatic intermittent hematuria after foam sclerotherapy that resolved over several days.

Figure 3 shows the changes in patient-reported outcome symptoms after foam sclerotherapy (n = 56). Among 33, 18, and 22 patients who had flank/back pain, abdominal pain, and abdominal distension before foam sclerotherapy, 70% (23/33), 78% (14/18), and 59% (13/22), respectively, experienced improvement in symptoms. None, mild, moderate, and significant refer to the degree of improvement in symptoms. Abbreviation: NBS, no baseline symptoms.
baseline total kidney volume \((r = -0.509, P = 0.002; r = -0.470, P = 0.005; r = -0.503, P = 0.002,\) respectively). Although kidney function remained stable or continued to decline for most patients, 4 (6%) patients with moderate total kidney volume (median, 1,440 [IQR, 1,050-1,800] mL) showed a sustained improvement in measured creatinine clearance ≥10 mL/min at least 12 months after foam sclerotherapy (Table 3).

### Illustrative Case Examples

**Figure 4** provides examples of 2 patients who experienced an improvement in pre–foam sclerotherapy–measured creatinine clearance for at least 10 mL/min. Patient 1 was a woman in her 30s with a protein-truncating PKD1 mutation who had successful ablation of a very large right central kidney cyst (Fig 4A). Baseline total kidney volume (1,071 mL) decreased by 29.5% and creatinine clearance increased by 21 mL/min 14 months after foam sclerotherapy. Similarly, patient 2 was a woman in her 40s with a PKD2 mutation who had successful ablation of a large lower-pole cyst in the right kidney (Fig 4B). Baseline total kidney volume (1,798 mL) decreased by 5.4% and creatinine clearance increased by 29 mL/min 17 months after foam sclerotherapy.

**Figure 5** provides examples of 2 patients with no improvement in GFR after foam sclerotherapy, possibly due to advanced chronic kidney disease. Patient 1 was a man in his 50s with a PKD2 mutation who had successful ablation of 1 large cyst in each kidney (Fig 5A). Baseline total kidney volume (4,727 mL) decreased by 13.4%, but there was no change in creatinine clearance. Patient 2 was a man in his 60s with a PKD2 mutation who had successful ablation of 1 large right mid-pole kidney cyst (Fig 5B). Baseline total kidney volume (2,066 mL) decreased by 7.6%, but creatinine clearance continued to decline. Both patients had advanced parenchymal disease shown by their kidney imaging and measured creatinine clearance < 40 mL/min before foam sclerotherapy.

### Potential Applicability to a General PKD Cohort

Although most detectable kidney cysts by MRI range from 3 mm to 3 cm in diameter, 1 or more large kidney cysts (≥5 cm in diameter) may be found in >50% of patients with ADPKD. In a subgroup analysis of 169 patients from the TGESP who underwent MRI,\textsuperscript{17} we found that 91 (53.8%) patients had at least 1 kidney cyst ≥5 cm; 58 (34.3%) had at least 2 large kidney cysts, and 25 (14.7%) had 4 or more large kidney cysts. Compared with patients without large kidney cysts, those with large kidney cysts were significantly older with higher median serum creatinine level (1.0 [IQR, 0.8–1.1] vs 0.8 [IQR, 0.7–1.0] mg/dL; P = 0.002) and total kidney volume (1,180 [IQR, 869–2,240] vs 552 [IQR, 444–823] mL; P < 0.001), but no difference in their mutation spectrum for ADPKD (Table 4).

### DISCUSSION

The mechanisms of disease progression in ADPKD are not well understood. However, total kidney volume has been
shown to be a well-validated predictor for subsequent decline in GFR.\textsuperscript{3,4,21,22} Similarly, kidney blood flow, which declines early in the clinical course, is also an independent predictor of progression in ADPKD.\textsuperscript{5,6} Notably, there is a strong inverse relationship between total kidney volume and kidney blood flow.\textsuperscript{6} Large kidney cysts (≥5 cm in diameter), though they are few in number, can be especially deleterious by impeding blood and urine flow in many nephrons over a large region.\textsuperscript{7} Therapies targeting total kidney volume expansion are currently thought to provide the most promising approach in slowing progression in ADPKD. Although tolvaptan has been shown to slow the rate of total kidney volume expansion and GFR decline,\textsuperscript{8,9} there is presently no therapy for kidney volume reduction in ADPKD.

In this feasibility study, we have shown that foam sclerotherapy is a minimally invasive procedure that is highly effective for experimental kidney volume reduction.

Figure 4. Case examples illustrate improved kidney function postsclerotherapy. (A) Successful ablation of a very large right midpole kidney cyst with improved creatinine clearance (CrCl) consistently up to 14 months after the procedure. (B) Successful ablation of a large right lower pole kidney cyst with improved creatinine clearance 17 months after the procedure. Abbreviations: FS, foam sclerotherapy; MRI, magnetic resonance imaging; PT, protein-truncating; TKV, total kidney volume.
in select patients with ADPKD. In our cohort, foam sclerotherapy reduced the targeted kidney volume by 22%, while nontargeted kidney volume expanded by 3% over a mean of 14 months; 57.6% and 27.3% of our patients experienced >20% and between 10% and 20% volume reduction of the targeted kidney at least 3 months after the procedure. Visual inspection of the targeted kidney cysts showed no change in size up to 12 months postprocedure, suggesting permanent ablation of the targeted cysts in a majority of patients.  

Although 13 (20%) patients reduced their MCIC risk class by at least 1 class and a small number of patients (6%) had a sustained improvement in creatinine clearance, these findings should be regarded as exploratory because our study was not formally designed to assess the treatment effect of foam sclerotherapy on kidney function. However,
we found foam sclerotherapy to be safe and well tolerated with low risk for serious complications.

Among the different sclerosants used for symptomatic ablation of large kidney and liver cysts, ethanol was frequently used in the past due to its low cost, easy accessibility, and a relatively high reported success rate. However, its use as a sclerosant has fallen out of favor due to a failure rate > 30%, necessitating multiple sessions of repeat treatment, which is associated with increased risk for severe pain from ethanol leakage into the retroperitoneum and subsequent tissue necrosis. Other potential complications of ethanol treatment include fever, intoxication, shock, and fibrosis of the ureteropelvic junction.

In comparison, sodium tetradecyl sulfate is an anionic surfactant that is clinically approved and widely used for treatment of varicose veins; direct instillation of sodium tetradecyl sulfate within kidney cysts is believed to destroy the blood vessels of cystic epithelia. Possible sodium tetradecyl sulfate–related adverse events include local pain,
Table 4. Characteristics of Patients With 1 or More Large Kidney Cysts From the Toronto Genetic Epidemiology Study of PKD

| Age, y | Cysts < 5 cm (n = 78) | Cysts ≥ 5 cm (n = 91) | P  |
|-------|----------------------|----------------------|----|
|       | 34.0 ± 10.0          | 45.0 ± 13.0          | <0.001 |
| Men   | 35 (45%)             | 49 (54%)             | 0.3 |
| Serum creatinine, mg/dL | 0.8 [0.7-1.0] | 1.0 [0.8-1.1] | 0.002 |

| Total kidney volume, mL | 552 [444-823] | 1,180 [869-2,240] | <0.001 |

| Mutation class | PKD1 protein-truncating (or in-frame in-del) | PKD2 non-protein-truncating | PKD2 | No mutation detected |
|----------------|---------------------------------------------|-----------------------------|------|----------------------|
|                | 28 (35.9%)                                  | 24 (30.8%)                  | 17 (21.8%) | 9 (11.5%) |

|                | 26 (28.6%)                                  | 21 (23.1%)                  | 30 (33.0%) | 14 (15.4%) |

Note: Data are expressed as number (percent), mean ± standard deviation, or median [interquartile range]. Conversion factor for units: serum creatinine in mg/dL to μmol/L × 88.4. Abbreviation: PKD, polycystic kidney disease.

*At least 1 cyst ≥ 5 cm.

hypersensitivity reactions, and tissue necrosis following extravasation (product monograph, Tromboject; Omega). In this regard, we did not observe any allergic reactions, but the painful episodes were likely caused by minor extravasation. However, the likelihood of sodium tetradecyl sulfate leakage is minimized by mixing it with air to create a viscous foam and by aspiration of the foam before removing the drains (see Methods for more details). Compared to ethanol, sodium tetradecyl sulfate foam sclerotherapy is associated with less pain, both in frequency and severity. In our cohort, the frequency of local abdominal or flank pain was 14%; all symptoms responded promptly to analgesia or resolved spontaneously, and none persisted for more than 7 days except in 2 patients, 1 of whom was thought to have neuropathic pain, while the cause of the other patient’s pain was not established. Two patients were complicated by foam sclerotherapy–associated pyelonephritis or cyst infection; all responded to antibiotic treatment.

The notion of decompressing cystic kidneys to slow progression in ADPKD was tried 3 decades ago in a study of surgical cyst fenestration, an invasive open procedure associated with significant risks for complications. Surgical cyst decompression performed in 16 patients with moderate to advanced chronic kidney failure (mean serum creatinine, 3.2 [range, 1.6-6.0] mg/dL) was effective in relieving kidney pain but not in improving kidney function. However, the presence of advanced parenchymal disease in these patients made it difficult to assess the potential of cyst decompression as a therapeutic approach to slow progression, especially in earlier stages of ADPKD. Nevertheless, cystic kidney–related discomforts such as abdominal/flank pain and/or distention were improved in >60% of our patients.

Although we found that foam sclerotherapy was effective in relieving “mass effect” symptoms, our study was not designed to test whether cyst decompression could delay PKD progression. Nonetheless, we were encouraged by 4 patients who showed a significant and sustained improvement in creatinine clearance after foam sclerotherapy. However, it is also clear that most patients with a baseline creatinine clearance ≤ 60 mL/min showed very modest or no changes in GFR after foam sclerotherapy. However, our study cohort comprised a heterogeneous group of patients with chronic kidney disease stages 1 to 5. Thus, a lack of change in kidney function might be due to: (1) insensitivity of creatinine-based GFR measurements in patients with normal or near-normal kidney function, (2) inadequate sclerotherapy to ablate all large kidney cysts (some might be too deep and not safely accessible), and (3) advanced disease with mostly scar tissue and little functional parenchyma. Overall, our impression is that patients with estimated GFRs of 60 to 90 mL/min and a few large and easily accessible cysts may be most likely to benefit from foam sclerotherapy to slow PKD progression.

In conclusion, 3% sodium tetradecyl sulfate foam sclerotherapy is an effective, safe, and well-tolerated minimally invasive experimental procedure for cystic kidney volume reduction and amelioration of “mass effect” symptoms in select patients with ADPKD. The availability of this promising approach in major medical centers with interventional radiology expertise provides an opportunity for the PKD research community to re-examine the potential therapeutic role of cystic kidney decompression in a more definitive manner. Future controlled studies using accurate measurements of GFR and kidney blood flow are needed to formally test whether cystic compression can be exploited to slow PKD progression and identify the subgroup(s) of patients who are most likely to benefit.

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