REVIEW ARTICLE

Acute Kidney Injury Post Cardiac Catheterization: Does Vascular Access Route Matter?

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Abstract: ***Background***: Acute Kidney Injury as a complication of cardiac catheterization is associated with increased length of hospital stay and mortality. In recent years, the use of the radial artery for cardiac catheterization is increasing in frequency.

Objective: The objective of this concise review was to evaluate the method of cardiac access site and its impact on Acute Kidney Injury following cardiac catheterization.

Methods: After a thorough search on Medline, Google Scholar and PubMed, we included all the literature relevant to Acute kidney injury following transradial and transfemoral cardiac catheterization.

Results: While acute kidney injury was caused due to a variety of reasons, it was important to consider each case on an individual basis. We found a trend towards increased use of transradial approach in patients at high risk of developing kidney injury. However, limitations such as operator experience, anatomical challenges and so on do exist with this approach.

Conclusion: Transradial access offers several advantages to a patient at high risk of acute kidney injury undergoing cardiac catheterization. Further large studies are needed to establish this trend in the years ahead.

Keywords: Transradial, transfemoral, catheterization, kidney injury, vascular access, anatomical challenges.

1. INTRODUCTION

The development of Acute Kidney Injury (AKI) following cardiac catheterization or Percutaneous Coronary Interventions (PCI) is a serious complication. Around 10% to 15% of patients develop AKI after coronary interventions [1]. The mechanisms by which patients develop AKI following an angiographic procedure are multifactorial. These occur from a combination of contrast-induced acute kidney injury (CI-AKI), atheroembolic kidney disease, and ischemic kidney injury in the setting of hemodynamic instability during the procedure [1-4]. AKI as a complication of cardiac catheterization, not only results in significantly increased costs and length of hospital stay but is also associated with increased short as well as long-term mortality [5-7].

Although the femoral artery has traditionally been the route of access for cardiac catheterization, more recently, the use of the radial artery for cardiac catheterization is increasing in frequency. One recent report found that Trans-Radial (TR) access was used in over two-thirds of cases [8, 9].

Despite being more technically challenging, peri-procedural patient comfort is significantly increased in this method [10]. More recently the landmark Acute Kidney Injury- Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox Trial (AKI-MATRIX) demonstrated a renoprotective effect using the TR approach [11]. In this focused review, we summarize the effect of vascular access route during cardiac catheterization and its impact on kidney function.

After a thorough search on Medline, Google Scholar and PubMed where studies through August 2018 were searched and all literature relevant to Acute kidney injury following transradial and transfemoral cardiac catheterization was included.

2. PATHOPHYSIOLOGY OF AKI DEVELOPMENT POST CATHETERIZATION

AKI is defined as an acute rise in serum creatinine by 0.3 mg/dL within 48 hours, an increase to 1.5 times the baseline creatinine within one week of index event, or a urine volume <0.5ml/kg/hour for 6 hours [12]. Development of cardiac catheterization-related AKI is multifactorial and can be influenced by a myriad of factors, most of which can be classi-

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fied as pre-procedural, intra-procedural, or post-procedural [4]. Pre-procedural risk factors include patient characteristics such as preexisting Chronic Kidney Disease (CKD), hydration status, age, and comorbidities such as diabetes, heart failure, peripheral arterial disease and Chronic Obstructive Pulmonary Disease (COPD) [4, 13]. Intra-procedural risk factors include the need for transfusions or intraoperative bleeding, hypotension, use of nephrotoxic contrast media, route of vascular approach, use of Intra-Aortic Balloon Pump (IABP), cardiogenic shock, and ST-elevation myocardial infarction (STEMI) on presentation [4, 13]. Post-procedural factors include post-operative anemia (largely reflective of intraoperative bleeding) and length of ICU stay [4].

Atheroembolic disease, CI-AKI, and hemodynamic instability represent the major pathways towards the development of de novo AKI after cardiac catheterization as shown in Fig. (**1**). Cholesterol embolization to the kidneys occurs more commonly in the Transfemoral (TF) approach owing to the passage of catheters through the descending aorta enroute to the heart [14]. This results in mechanical embolization of cholesterol crystals, with resultant occlusion of the renal arterioles and glomerular capillaries causing kidney injury. Femoral access has historically been preferred because of the larger size catheters and sheaths that its use permits [15]. It has been shown that the use of large lumen guiding catheters is associated with increased risk of scraping debris and hence subsequent atheroembolization [16]. On the other hand, radial access has the advantage of using smaller sized sheaths and catheters, although this is a double-edged sword [15]. The radial approach also has the advantage of avoiding passage through the potentially atheroma rich aorta and renal vessels, thereby decreasing chances for embolization [17].

TR vascular access has been found to have a significant reduction in major bleeding leading to a reduced risk of hemodynamic instability and less ischemic injury to the kidney [18]. This is significant to consider because vascular access site-related bleeding accounted for over half of the bleeding complications post catheterization [19]. Achieving hemostasis with a femoral puncture site is more challenging due to its anatomic location. Pressure below the optimal site can lead to ineffective compression against the femoral head, whereas pressure above the optimal site, where the artery runs predominantly retroperitoneal, can also lead to poor hemostasis and may result in retroperitoneal bleeding [20]. The location of the femoral puncture site, whether low or high, was associated with up to 70% of all vascular access complications in one study [21]. In contrast, the radial artery site is more superficial and readily accessible to compression, so hemostasis can be achieved without the introduction of a foreign body such as a vascular closure device [22]. The Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome (RIFLE-STEACS) study demonstrated that the use of TR access reduced clinically relevant access site bleeding by over 60% with a corresponding decreased need for transfusion [23]. This is significant as the need for transfusion was identified as the strongest risk factor for post catheterization AKI among patients with diabetes and normal baseline kidney function [24].

CI-AKI represents another important pathway for the development of post-catheterization AKI. Several patients and procedural risk factors are known to be associated with an increased risk of CI-AKI [25]. CI-AKI develops due to a combination of renal medullary hypoxia from alterations in the levels of vaso-reactive factors and from free radical-mediated injury from contrast exposure [25, 26]. Given the confounding nature of operator expertise, conflicting reports
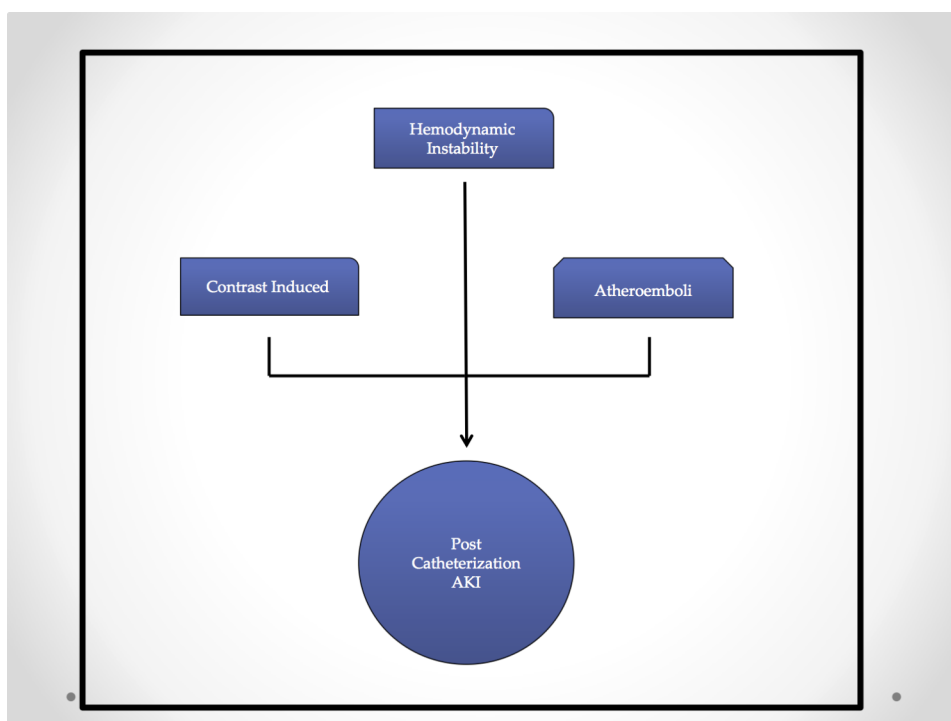
Fig. (1). Factors responsible for Post catheterization AKI.

exist regarding the amount of contrast used based on the method of access [17]. However, a recent prospective propensity-matched trial done in patients with STEMI who received either a PCI or thrombolysis or conservative management which showed no difference in the rates of AKI in patients who did or did not receive contrast [27]. Thus, conflicting evidence continues to emerge on the effects of contrast on renal function. A detailed synopsis of the pathophysiology of CI-AKI is beyond the scope of this review.

3. RADIAL VERSUS FEMORAL ACCESS IN CORONARY ARTERY DISEASE (CAD): FROM OBSERVATIONAL STUDIES TO RANDOMIZED CLINICAL TRIALS

Although various studies have been done to compare both TR and TF vascular access, not many studies have looked specifically at their effect on renal function. Vuurmans *et al*. found in a retrospective analysis of large British registry of over 60,000 patients, that a TR approach was associated with less risk of developing Chronic Kidney Disease (CKD) within 6 months [17]. However, in this study, the population that underwent a TF approach had higher comorbidities and a lower baseline Glomerular Filtration Rate (GFR) to begin with [17]. A retrospective analysis of a large registry in Japan was done analyzing the impact of periprocedural bleeding on CI-AKI post-catheterization. They found that CI-AKI was more likely to develop in patients with major bleeding complications and correlated with the degree of hemoglobin drop (OR 2.23; CI [1.37-3.63]; p=0.001) [28]. Of note, they found that CI-AKI was more common in the TF intervention group; however, the majority of the patients in this study had TF interventions making comparisons difficult [28]. Therefore, additional work was needed to prove the conclusion that TR access results in decreased AKI. This was thought to be due to the fact that TR has less vascular and/or major bleeding complications.

A retrospective propensity-matched study was using the Blue Cross Blue Shield of Michigan Cardiovascular Consortium involving over 80,000 patients showed that the TR approach had lower risk of AKI even after adjustment for periprocedural bleeding (OR 0.76 (*P*=0.03)), with periprocedural bleeding in itself being independently associated with AKI (OR, 2.86; CI [1.75-4.66]; P<0.001) [29]. Another retrospective propensity-matched analysis involving mainly high-risk patients in high volume centers undergoing primary PCI for STEMI showed that TF group was associated with a higher risk of AKI (OR 1.65; CI [1.084-2.524]; p=0.02). In this study, contrast use was significantly less with the TF group (188.9±71.6 *vs*. 207.0±73.6, p <0.0001) [30] suggesting other mechanisms in play leading to the AKI risk aside from contrast alone. Finally, a prospective (high volume radial) single-center study using stricter criteria for the definition of AKI found that although AKI was lower in TR compared to TF (2.5% *vs*. 4.5%, p<0.001), after adjusting for other confounders, it was no longer significant [31].

A subanalysis of a study was done to evaluate the amount of contrast related to the incidence of AKI among STEMI patients which showed a nonsignificant trend toward reduced CI-AKI with radial access (OR, 0.27; 95% CI, 0.07-1.05;P=0.06) [32]. In 2015, a meta-analysis was done including all the observational studies available at that time comparing radial versus femoral access [33]. Utilizing a sample total of over 20,000 patients included in the meta-analysis, there was less risk of AKI, favoring the radial approach (RR 0.52, 95% CI [0.38-0.73], p < 0.001) [33]. Some of the limitations in this meta-analysis were the individual studies themselves, as they were all observational. At the same time, there were different characteristics of the study population, with some populations predominantly presenting as STEMI, and lastly the lack of a standard definition of AKI amongst the studies.

Several recent retrospective studies analyzed the effect of vascular access site on renal outcomes and are summarized in Table **1**. One retrospective study done by Feldkamp *et al*. included consecutive patients who underwent catheterization regardless of reason (whether acute coronary syndrome (ACS) or not) to mimic real-world conditions. They found that radial access led to less risk of AKI (OR 0.65 (CI [0.51-0.83] <0.001). What was unique about this study was the subgroup analysis for patients with ACS and baseline CKD who were deemed at greater risk for AKI to begin with, had a stronger reduction in risk with TR [OR 0.52 (CI [0.34-0.81] p=0.003)] *vs*. TF [0.60 (CI [0.41-0.87] p= 0.007)] [34]. This implies that the higher the risk for AKI the higher the potential benefit in terms of vascular access effect on kidney function. Another retrospective study by Vora *et al*. in 2017 found similar results in the presence of baseline CKD. The initial hypothesis for this study was that patients with baseline CKD had a higher risk of bleeding complications and AKI, and that the more advanced the CKD, the higher the risk for both. Eventually, this study found that although fluoroscopy time was longer in the TR approach, the amount of contrast used was not different than TF. There was also a significantly lower rate of transfusion with the effect more pronounced with more advanced CKD stage (OR 0.43 CI [0.2-0.9] for those with GFR 15-29). In addition, among all patients, the risk for dialysis was also lower with the effect extending even to those with baseline CKD with an OR 0.80 (CI [0.68-0.94]; P=0.008) [35].

Two similar retrospective propensity-matched studies also recently came out from single centers in efforts to identify and help determine the relationship of vascular access to AKI using existing real-world single center hospital registries. The study done in Pennsylvania used the AKI definition of both >0.5 mg/dl or >25% increase in serum creatinine level from baseline at 48 to 72 hours after the catheterization and also observed decreased rates of AKI with TR access with OR 0.57 (CI [0.35-0.91] p= 0.018) [36]. In contrast, the study conducted out of Washington used different criteria for AKI defined as an increase of ≥0.3mg/dL post catheterization or 25% reduction of creatinine clearance. They found a strikingly different incidence rate of approximately 17% and found a decrease in AKI after TR access with OR 0.28 (CI [0.19-0.59], p<0.001) [37]. This presents a common theme seen in previous studies where the lack of a standardized AKI definition, makes it harder to incorporate all the conflicting results into a single meta-analysis. It is worthwhile to note that a recent study which looked into different definitions for AKI post catheterization and mortality showed that the incidence of CI-AKI is somewhere between 6 to 15.7%. Here, AKI was defined as an absolute increase in serum

Table 1.   The effect of access site on Renal outcomes.

Authors	Year	Type of Study	Number of Patients (n)	Femoral Approach (n)	Radial Approach (n)	Radial AKI (%)	Femoral AKI (%)
Vuurmans [17]	2010	Retrospective Cohort	69214	54144	13680	0.50	2.20
Ohno [28]	2013	Retrospective Cohort	2564	1916	648	5.56	13.99
Kooiman [29]	2014	Retrospective Cohort	17714	8857	8857	1.43	1.94
Damluji [31]	2014	Retrospective Cohort	1254	521	733	2.46	4.41
Andò [32]	2014	Retrospective Cohort	126	60	66	4.55	15.00
Cortese [30]	2014	Retrospective Cohort	450	225	225	8.44	16.89
Hamon [45]	2015	Retrospective Cohort	3957	2497	1460	5.96	10.85
Kolte [48]	2016	Retrospective Cohort	1162	857	305	5.90	7.00
Feldkamp [34]	2017	Retrospective Cohort	2937	1796	1141	10.10	15.90
Steinvil [37]	2017	Retrospective Cohort	6743	5624	1,119	4.70	13.10
Pancholy [36]	2017	Retrospective Cohort	7529	5353	2176	1.10	2.40
Ando [11]	2017	Randomized Controlled Trial	8210	4101	4109	15.43	17.36
Barbieri [39]	2018	Retrospective Cohort	4199	2284	1915	13.20	11.70

Acute Kidney Injury - Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox Trial (AKI-MATRIX)
First pre-specified, large randomized controlled trial that prospectively analyzed the incidence of AKI in radial versus femoral access.
Overall incidence of AKI was significantly reduced with the use of radial access.
Utilizing radial access had a statistically significant benefit in patients at highest risk for AKI (Mehran score >10).
Bleeding minimization in radial access as opposed to femoral access was associated with a reduced risk of AKI.

Fig. (2). AKI-MATRIX.

creatinine of >0.5 mg/dL (44 mmol/L) or 0.3mg/dL (27 mmol/L), in line with most of the studies above. In this recent study, mortality risk was predicted based on the AKI definition used [38]. A recent single-center retrospective study involving over 4000 patients failed to demonstrate an association between CI-AKI and angiographic approach, despite adjusting for confounders [39].

This affirms that the usual definitions for AKI used in past studies can serve as good predictors of outcomes such as mortality and likely reflects an accurate assessment of renal function.

4. AKI-MATRIX

The first large, pre-specified, multi-center, randomized controlled MATRIX [40] trial described data in 8000 patients randomized to either TR or TF access. A subanalysis called AKI-MATRIX included several definitions of AKI, including absolute (>0.5 mg/dl) or a relative (>25%) increase in serum creatinine, which was incorporated into this intention to treat trial. Baseline pre-procedural GFR was comparable for both groups. A >25% increase in serum creatinine was observed in 15.4% with TR and 17.3% with the TF group (RR 0.87 CI [0.77 to 0.98]; p= 0.0195), and a >0.5 mg/dl absolute increase in serum creatinine was observed in 4.3% in the TR group vs 5.4% in the TF group (RR 0.77, CI [0.63-0.95]; p= 0.0131) [11] (Fig. **2**). This beneficial effect was further increased among patients deemed at higher risk for AKI, including those with ACS and reduced GFR specifically KDIGO 3, high Mehran score, and advanced Killip class. Multivariate analyses performed with the individual components of the Mehran score (risk factors for CI-AKI), resulted in TR access retaining its significance in predicting subsequent AKI. However, when the multivariate analysis was done together with bleeding, hemoglobin levels, and the need for blood transfusions, TR was no longer significant. However, TR did exhibit a trend towards significance, while bleeding, hemoglobin and transfusions (bleeding related parameters) exhibited a two to three-fold risk of AKI [11]. This implies that a majority of the effect of a TR approach in reducing AKI is predominantly from a reduction in periprocedural bleeding. Bleeding might not be the only driving factor for AKI in this patient population. Atheroembolism might still play a role as its incidence in patients undergoing angiography can range from 18 to 96% in some studies [3].

5. LIMITATIONS OF THE TR APPROACH

TR interventions, however, are not without limitations. Operator skill as stated previously plays a significant part in these interventions, although, familiarity with the use of TR access is increasing. Further, utilizing the upper extremity arteries could potentially be detrimental to future fistula placement and maturation [41]. Given that a significant proportion of these patients may have underlying CKD, a pre-procedural discussion is most certainly warranted. As of now, no large studies have addressed the potential detrimental effects of radial access on subsequent Arteriovenous Fistula (AVF) creation. Another limitation is the issue of multiple punctures causing subsequent radial artery stenosis with resultant difficulty in reusing the same radial site in future PCIs [42]. Complex coronary artery lesions such as complex bifurcation lesions that require larger catheter sheaths and PCI on bypass grafts are more readily accessible/feasible *via* femoral access [43]. Possible use of the radial artery as a graft for coronary bypass surgery should also be taken into consideration as the radial artery has similar outcomes compared to the left internal mammary artery [44]. Lastly, there are concerns of increased risk of stroke with the TR approach due to anatomic proximity, increased catheter exchanges due to the small caliber, and longer procedure times. A trial in 2012 comparing TR with TF access found nominally higher, but not statistically significant rates of strokes detected by magnetic resonance imaging (MRI) (17.5% *vs.* 11.7%, p = 0.31) [45]. However, a recent meta-analysis of 11,000 patients and 13 studies found no significance between the risk of stroke between TR and TF [46].

Additional causes of TR failure as described by Dehghani *et al.*, can be observed in elderly patients over 75 years of age, prior to the coronary artery bypass graft surgery, and short stature [47]. Lastly, anatomical abnormalities in the upper extremity arterial system, although a rare occurrence, pose contraindications to TR access.

CONCLUSION AND FUTURE DIRECTIONS

Each case should be undertaken on an individual basis, but it is clear that there are several advantages when utilizing TR access. For patients at high risk of AKI, TR approach is probably preferable, presuming operator competency [48]. More extensive studies are needed to confirm whether TR intervention does, in fact, prevent or hinder fistula formation if a future need for dialysis develops. More work is needed to understand the incidence of renal atheroembolic events during PCI as a cause of procedural AKI. At the same time, there should be a continued search for other factors that can contribute to AKI. This will help reduce the morbidity and cost of care for AKI in the setting of cardiac catheterization while optimizing coronary revascularization outcomes.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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