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Impact of vascular access on the development of contrast induced nephropathy in patients undergoing coronary angiography and/or percutaneous coronary intervention

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ABSTRACT

Background: Contrast induced nephropathy (CIN) is a common complication of procedures that foresee the use of contrast media. Several risk factors have been identified as independent predictors of CIN, but, to date, no definitive data are available about the association between the angiographic approach and its development.
Methods and results: Our population included 4199 patients undergoing coronary angiography and/or PCI. CIN was defined as an absolute ≥0.5 mg/dl or a relative ≥25% increase in creatinine level at 24–48 h after the procedure without another clear cause for the acute kidney injury. The total incidence of CIN was 12.4%. We divided our population into two groups, according to the angiographic approach: transradial (TR) $n = 1915$ or transfemoral (TF) $n = 2284$. Patients treated with TR approach were more often males, with history of hypertension, and PCI, but less often diabetic, with previous myocardial infarction, coronary artery by-pass graft surgery and cerebrovascular accident. They had a higher ejection fraction, higher prevalence of PCI, elective indication but interestingly a lower amount of contrast volume. Patients treated with TR approach had higher platelets, Total, LDL and HDL cholesterol, but lower triglycerides, glycaemia and basal creatinine. No significant difference was observed between the two groups regarding the development of CIN (TR 13.2% vs TF 11.7%, $p = 0.16$). The absence of association between angiographic approach and the incidence of CIN was also confirmed at multivariate analysis after correction for baseline confounders (Adjusted OR [95% CI] = 1.2 [0.97–1.50], $p = 0.09$) and at subgroup analysis according to main risk factors for CIN. Similar results were obtained dividing our population according to propensity score tertiles: 1st Tertile CIN (TF 8.8% vs TR 8.9%), $p = 0.95$; OR (99% CI) = 1.01 (0.96–1.48), $p = 0.95$, 2nd Tertile CIN (TF 10.8% vs TR 12.4%), $p = 0.35$; OR (99% CI) = 1.17 (0.84–1.62), $p = 0.35$, and 3rd Tertile CIN (TF 15.6% vs TR 17.2%), $p = 0.41$; OR (99% CI) = 1.12 (0.85–1.48), $p = 0.41$.
Conclusion: This is the first large study showing the absence of relationship between the angiographic access and the incidence of CIN.

1. Introduction

Contrast induced nephropathy (CIN) is one of the most common complications of procedures that foresee the use of contrast media [1,2] and is commonly defined as an increase in serum creatinine levels, usually >0,5 mg/dl or 25% of baseline levels, within 24–48 h after contrast exposure. The development of CIN after coronary angiography or angioplasty is associated with a poor long-term clinical outcome [3]. In patients undergoing diagnostic and/or therapeutic coronary angiography CIN has shown to occur in up to 20–25% depending on the presence of known risk factors. The most important recognized risk factors for the development of CIN can be divided into two groups: patients' related risk factors (chronic renal failure, diabetes, older age, hyperuricaemia, anaemia, dehydration, hypoproteinaemia, previous kidney transplant and the use of nephrotoxic drugs such as diuretics or aminoglycosides) and procedural related risk factors (contrast volume and contrast media characteristics, two or more consecutive procedures within 72 h, the use of intra-aortic balloon pump) [4–6]. Several additional studies have been conducted to identify new risk factors associated with this complication [7–10]. However, few data are available at the moment about the relationship between the vascular access and the development of CIN. In fact, some studies have

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assessed the possible contribution of atheroembolism in the development of acute renal failure with trans-femoral (TF) access potentially explained by its proximity to renal arteries [11]. From the theoretical point of view the trans-radial (TR) approach, following a different path to coronary arteries, could be associated with a lower incidence of CIN, as some demographic registries have recently shown [12,13]. Moreover, periprocedural bleeding, which has been shown to be consistently reduced by radial approach [14], has been identified as a possible risk factor for the development of CIN. Therefore, the aim of the current study was to evaluate the role of the vascular access on the development of CIN among a large cohort of patients undergoing coronary angiography and/or PCI.

2. Material and methods

Our population is represented by consecutive patients undergoing coronary angiography and/or angioplasty at Catheterization Laboratory of AOU Maggiore della Carità, Novara, from January 2007 to January 2016. Informed consent was obtained by all patients before angiography. Hypertension was defined as systolic pressure >140 mm Hg and/or diastolic pressure >90 mm Hg or if the individual was taking antihypertensive medications. All patients with creatinine clearance <60 ml/min were hydrated with saline solution 1 ml/kg/h 12 h before and after the procedure or with saline solution 0.5 ml/kg/h, if ejection fraction ≤40% or with sodium bicarbonate (154 mEq/l in dextrose and water received 3 ml/kg for 1 h before contrast exposure followed by an infusion of 1 ml/kg/h for 6 h after the procedure) for emergency PCI. CIN was defined as an absolute ≥0.5 mg/dl or a relative ≥25% increase in the serum creatinine level at 24 or 48 h after the procedure without another clear cause for the acute kidney injury.

2.1. Biochemical measurements

Blood samples were drawn at admission in patients undergoing elective (following a fasting period of 12 h) or urgent coronary angiography. Glucose, creatinine, uric acid, blood cells count and lipid profile were determined by standard methods.

Creatinine was measured at 12, 24 and 48 h after the procedure or longer in case of development of CIN.

2.2. Coronary angiography

Coronary angiography was routinely performed by the Judkins technique using 6-French right and left heart catheters. Angiographic approach was at the discretion of the interventional cardiologist, but in last five years our standard approach is the radial one in >95% of cases. Quantitative coronary angiography (Siemens Acom Quantcor QCA, Erlangen, Germany) was performed by two experienced cardiologists who had no knowledge of the patients' clinical information. Significant coronary artery disease was defined as at least 1 coronary stenosis >50%. The contrast medium used was non-ionic, low osmolality (Optiray-Ioversol, 350 mg/ml, Ultravist-Iopromide, 370 mg/ml, Visipaque-Iodixanol, 320 mg I/ml).

2.3. Statistical analysis

Statistical analysis was performed with the SPSS 17.0 statistical package. Continuous data were expressed as mean ± SD and categorical data as percentage. Analysis of variance and the chi-square test were used for continuous and categorical variables, respectively.

In order to overcome the potential bias due to differences in baseline and angiographic or procedural characteristics, we additionally performed a propensity score analysis. Briefly, for each patient a propensity score was calculated by the use of forward logistic regression analysis, that identified variables independently associated with radial approach. Patients were subsequently divided in tertiles of the propensity score. The impact of radial approach on the occurrence of CIN was evaluated in all 3 subgroups of patients with similar characteristics among those patients undergoing radial or femoral approach.

Multiple logistic regression analysis was performed to evaluate the relationship between vascular approach and the development of CIN, after correction for baseline confounding factors (clinical and demographic variables with a p value <0.05), that were entered in the model in block.

3. Results

We analyzed a total of 5009 patients undergoing coronary angiography and/or angioplasty. A total of 810 patients were excluded because of end stage renal failure requiring dialysis or because serum creatinine at 24–48 h were not available. Therefore, our final study population was represented by 4199 patients, that were divided in two groups according to the angiographic approach (TF, $n = 2284$ and TR, $n = 1915$). Patients' baseline clinical and demographic characteristics, indication for angiography, procedural main characteristics, and admission therapy, according to angiographic approach, are listed in Table 1. Patients treated with TR approach were more often males ($p = 0.05$), with a previous history of hypertension ($p = 0.005$), and PCI ($p < 0.001$), but with less often history of diabetes ($p = 0.003$), previous myocardial infarction ($p = 0.04$), coronary artery by-pass graft surgery ($p = 0.001$) and cerebrovascular accident ($p = 0.02$). The two groups significantly differed for the indication to angiography and/or PCI ($p < 0.001$), with more ACS in the femoral group. Patients in the TR group had a higher ejection fraction ($p = 0.04$), higher prevalence of PCI after coronary angiography ($p < 0.001$), but interestingly lower amount of contrast volume during the procedure ($p < 0.001$) and they were more often in therapy with angiotensin receptor blockers ($p = 0.02$) and beta blockers ($p = 0.005$) but less often with nitrate ($p < 0.001$) and ADP receptor antagonist ($p < 0.001$). Most significant biochemical parameters according to angiographic approach are listed in Table 2. Patients treated with TR approach had higher platelets ($p = 0.003$), Total ($p < 0.001$), LDL ($p < 0.001$) and HDL ($p < 0.001$) cholesterol, but lower triglycerides ($p < 0.001$), glycaemia ($p < 0.001$), uric acid ($p = 0.03$) and basal creatinine ($p < 0.001$), with consequent higher creatinine clearance ($p < 0.001$). Baseline clinical and procedural characteristics among tertiles according to the propensity match are listed in Table 1 Supplementary. The total incidence of CIN in our population was 12.4% without any significant difference between the two groups (TR 13.2% vs TF 11.7%, $p = 0.16$) (Fig. 1). The absence of association between angiographic approach and the incidence of CIN was also confirmed at multivariate analysis after correction for baseline confounders (gender, hypertension, diabetes mellitus, history of myocardial infarction, previous PCI, previous CABG, previous stroke, ejection fraction, indication to angiography, therapy with ARB, nitrate, beta blockers, ADP antagonists, clopidogrel, PCI performed during procedure, contrast volume, white blood cells, platelets, total, LDL, and HDL cholesterol, triglycerides, glycaemia, creatinine, creatinine clearance and uric acid) (Adjusted OR [95% CI] = 1.19 [0.95–1.49], $p = 014$). Similar results were obtained dividing our population according to propensity score tertiles: 1st Tertile CIN (TF 8.8% vs TR 8.9%), $p = 0.95$; OR (99% CI) = 1.01 (0.96–1.48), $p = 0.95$, 2nd Tertile CIN (TF 10.8% vs TR 12.4%), $p = 0.35$; OR (99% CI) = 1.17 (0.84–1.62), $p = 0.35$, 3rd Tertile CIN (TF 15.6% vs TR 17.2%), $p = 0.41$; OR (99% CI) = 1.12 (0.85–1.48), $p = 0.41$. No significant differences between the angiographic approach and the development of CIN were found also at subgroup analysis (Fig. 2) according to main risk factors for CIN such as contrast volume (p int 0.29), ACS (p int 0.08), gender (p int 0.12), hypertension (p int 0.17), age (p int 0.13), diabetes (p int 0.11) and creatinine clearance (p int 0.10). Finally, our results were confirmed also among patients undergoing elective PCI (908 patients): CIN (TR 13.5% vs TF 10.5%, $p = 0.18$).

4. Discussion

The main finding of our study is that in patients undergoing coronary angiography and/or percutaneous interventions, vascular access does not have any impact on the development of CIN. Coronary artery disease is still the first cause of mortality in developed countries. However, a larger application of revascularization procedures, especially in the setting of acute myocardial infarction [15,16], has contributed to the relevant reduction in mortality observed in the last decades. Due to the improvement in adjunctive therapies and stent technologies [17–20], a yearly growing number of patients undergo percutaneous revascularization, with a larger proportion of high-risk patients [21,22], including those with impaired renal function. The development of CIN is associated with increased mortality and morbidity rate and is an expensive complication [23]. Even though CIN has traditionally been associated with higher procedural amount of contrast medium [24], the development of this complication after contrast medium administration in

patients undergoing angiography and/or PCI is multifactorial [5] and depends by the presence of patient-related and procedural-related risk factors. About procedural risk factors, the role of vascular access on the development of CIN is still controversial. TF approach implies the passage of catheters/guidewires through the abdominal aorta, close to renal arteries. Atheroembolism with cholesterol dislodgment from the aorta by the diagnostic or guiding catheters might represent a possible cause for the development of CIN [25]. Moreover, TF approach has been associated with a higher risk of bleedings, with consequent anaemia, hypotension and worsening of renal function [26,27]. TR approach is now becoming more popular and seems to be associated with less periprocedural complications such as bleeding complications. Moreover, following a different path to the coronary arteries, with consequent lower risk of cholesterol embolization, it might be associated with lower incidence of CIN. To date, only registries with an imbalanced distribution of the population have assessed a possible vascular access-related reduction in renal complications. In British Columbia Cardiac and Renal Registries [13], Vuurmans and colleagues showed that TF approach is associated with an increased risk of CIN with an OR of 4.36 (95% CI 2.48 to 7.66) for the development of the composite end point of new dialysis, new stage 4 or 5 chronic kidney disease (CKD) or new CKD. The PRIPITENA Urban Registry [28] confirmed these results among 450 STEMI patients undergoing primary PCI (OR 1.654, 95% CI 1.084 to 2.524). Similarly, a recent meta-analysis by Andò and colleagues underlined benefits of radial approach in reducing the incidence of CIN after PCI [29]. On the other hand an observational study by Samul and colleagues [30] showed benefits of the radial approach in terms of safety (local complications and bleeding) and comfort for patients. However, TR approach showed to need a larger amount of contrast volume and therefore should be used with more caution in patients with renal disease. To date, the majority of studies in literature are observational studies and registries with imbalanced patient distribution. In a recent substudy of a large randomized trial (AKI-MATRIX) [31], including 8404 patients, TR was associated with a significant reduction in the development of CIN (15.4% vs 17.4%, OR = 0.87 [0.77 to 0.98]; $p = 0.018$).

Our study includes a total of 4199 patients from 2007 to 2016, among whom we showed no differences between TR and TF approach on the development of CIN. The total incidence of CIN in our population was 12.4% without any significant difference between the two groups (TF 11.7% vs TR 13.2%, $p = 0.16$). The results were confirmed after adjustment for all confounding factors and in subgroups of high-risk patients. Interestingly, our results were confirmed also among a more homogeneous subgroup of patients undergoing elective PCI (908 patients, CIN: TR 13.5% vs TF 10.5%). The lack of correlation between the vascular access and the development of CIN, also in the absence of established risk factors for CIN in the acute setting, (haemodynamical instability, stress hyperglycaemia, unknown anaemia etc.) further strengthens our findings. The lower occurrence of CIN and the lower sample size, as compared to the AKI-MATRIX, may have contributed to a lower statistical power as compared to the MATRIX subanalysis. However, our findings may also potentially be

Table 1
Baseline clinical and procedural characteristics.

Baseline clinical and procedural characteristics	Femoral access ($n = 2284$)	Radial access ($n = 1915$)	p value
Age (Mean ± SD)	68.4 ± 7.1	67.8 ± 7.4	0.07
Male sex (%)	70	72.7	0.05
Hypertension (%)	71.8	74.5	0.05
Smokers			0.85
Active smokers (%)	20.4	22.8	
Previous smokers (%)	25.6	24.1	
Dyslipidaemia (%)	55.8	56.1	0.85
Diabetes (%)	36.3	31.8	0.003
Kidney transplantation (%)	0.3	0.4	0.99
Family history of CAD (%)	28.4	29.2	0.58
History of MI (%)	25.5	22.8	0.04
Previous PCI (%)	21.8	34.3	<0.001
Previous CABG (%)	13.1	10	0.001
Previous stroke (%)	7.7	5.8	0.02
Ejection fraction (Mean ± SD)	49 ± 13.2	49.8 ± 12.4	0.04
Indication for angiography			<0.001
Stable angina or silent ischaemia (%)	25.1	29.8	
Acute coronary syndrome (%)	55	47.1	
DCM or valvular disease (%)	19.9	23.1	
Therapy at admission			
ACE inhibitors (%)	38.6	36.5	0.16
ARB (%)	20.9	24	0.02
Nitrate (%)	38	32	<0.001
Beta blockers (%)	51.1	55.5	0.005
ASA (%)	59.1	58.2	0.57
ADP receptor antagonist (%)	24.3	17.3	<0.001
Clopidogrel (%)	21.5	3.9	<0.001
New ADP antagonists (%)	2.8	13.4	<0.001
Diuretics (%)	31	32.4	0.35
Statins (%)	49.3	50.5	0.42
Procedural characteristics			
PCI (%)	49.2	65.4	<0.001
Left main (%)	3.2	3.6	0.89
CTO (%)	7.5	6.4	0.56
Bifurcation (%)	29.4	30.5	0.45
Multivessel PCI (%)	28.8	27.1	0.32
Contrast volume (Mean + SD)	231.8 + 148.8	208.9 + 144.9	<0.001

SD = standard deviation; CAD = coronary artery disease; MI = myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery by-pass graft; DCM = dilated cardiomyopathy; ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blockers; ASA = acetylsalicylic acid.

Table 2
Biochemistry parameters.

Biochemistry parameters	Femoral access ($n = 2284$)	Radial access ($n = 1915$)	p value
Platelets (10^6/ml; Mean ± SD)	216.8 ± 66.5	223 ± 68.4	0.003
Haemoglobin (g/dl; Mean ± SD)	13.4 ± 1.7	13.3 ± 1.7	0.38
WBC (10^3/ml; Mean ± SD)	7.9 ± 3.3	8 ± 2.8	0.09
Total cholesterol (mg/dl; Mean ± SD)	159.9 ± 40	163.5 ± 43.1	0.006
HDL cholesterol (mg/dl; Mean ± SD)	39.4 ± 43	43 ± 12.8	<0.001
LDL cholesterol (mg/dl; Mean ± SD)	92 ± 35.7	95.9 ± 37.6	<0.001
Triglycerides (mg/dl; Mean ± SD)	147.7 ± 94	124.4 ± 69	<0.001
Glycaemia (mg/dl; Mean ± SD)	128.8 ± 51.2	123.3 ± 47.4	<0.001
Glycated haemoglobin (%; Mean ± SD)	6.3 ± 1.2	6.6 ± 1.1	0.65
Creatinine (mg/dl; Mean ± SD)	1.1 ± 0.38	1 ± 0.39	<0.001
Creatinine clearance (ml/min; Mean ± SD)	71.6 ± 29.5	82.8 ± 36	<0.001
Uric acid (mg/dl; Mean ± SD)	6.2 ± 1.8	6.1 ± 1.9	0.03

WBC = white blood cells; HDL = high density lipoprotein; LDL = low density lipoprotein; SD = standard deviation.

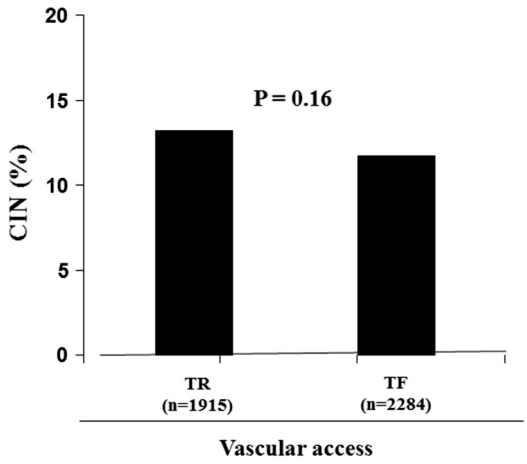

Fig. 1. Bar graph showing the relationship between vascular access and the risk of contrast-induced nephropathy.

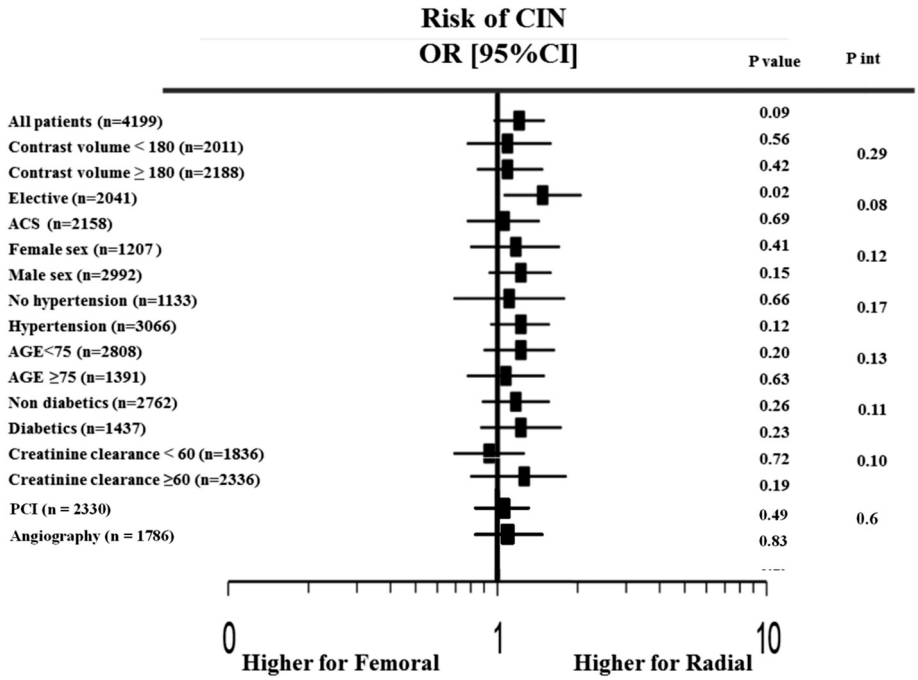

Fig. 2. Forrest plot showing the absence of relationship between angiographic approach and CIN among main risk known risk factors.

explained by the fact that with TR approach, even if a lower incidence of renal atheroembolism respect to TF approach may be expected, this complication may not be completely abrogated especially in patients with disease aortic arch.

Future large randomized studies are certainly needed to further investigate this relevant issue, that may further support the routine use of radial approach in the treatment of coronary artery disease.

5. Limitations

This was a prospective non randomized study with several differences in baseline characteristics among the two groups of patients. However, the results have been confirmed by multivariate adjustment to take into account all these differences. Even though the occurrence of CIN is commonly evaluated at 48 h, it may appear even later than this time threshold. Furthermore, we were not able to provide data on the progression of kidney failure at follow-up, being this disease chronically progressive. Finally, we did not routinely collected data that may affect the occurrence of CIN, such as hypoproteinaemia, decompensated heart failure at the time of angiography and intraaortic balloon pump implantation. However, our results were confirmed in the analysis restricted to patients undergoing elective PCI.

6. Conclusions

This is the first large study showing that among patients undergoing coronary angiography or percutaneous interventions the choice of the vascular access does not impact on the development of CIN.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.08.026.

Conflict of interest

The authors have no conflict of interest regarding the opinion expressed in this manuscript and did not receive grant or financial support from industry or from any other source to prepare this paper.

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Prof De Luca had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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