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ORIGINAL RESEARCH ARTICLE

Contrast-induced nephropathy after cardiac resynchronization therapy implant impairs the recovery of ejection fraction in responders

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Abstract

Aims Data regarding contrast-induced nephropathy (CIN) after cardiac resynchronization therapy (CRT) implant are limited. We aimed to investigate the incidence and determinants of CIN and its impact on CRT response and outcomes.

Methods and results Patients who underwent CRT implant were retrospectively analysed, and CIN was defined as an increase of serum creatinine ≥0.3 mg/dL or ≥1.5 times the baseline value. Response to CRT was defined as a reduction of left ventricle end-systolic volume (LVESV) of 15% or the increase of five percentage points in ejection fraction (EF) as assessed by echocardiography at 6 months. Follow-up visits were scheduled at 3, 6, and 12 months.

Contrast-induced nephropathy occurred in 13/107 patients (12%). Among baseline clinical, echocardiographic, and laboratory characteristics, only a high baseline serum creatinine was associated with the occurrence of CIN. Symptoms, EF, and LVESV at 6 months improved in both CIN and non-CIN patients, and the rate of responders to CRT was similar. Among responders, at 6 months, those with CIN had significantly lower EF (28.5% vs. 35.7% $P = 0.003$).

At a median follow-up of 112 weeks, 43% of patients experienced a clinical event with similar incidence in CIN and non-CIN patients, and likewise survival was similar. Non-responders to CRT had worse survival while among responders those with CIN had worse survival than non-CIN patients (71% vs. 90%, $P = 0.0035$).

Conclusions The incidence of CIN is rather high. Although CIN does not influence response to CRT overall, however among responders impairs the recovery of EF and survival.

Keywords Contrast-induced nephropathy; Heart failure; Cardiac resynchronization therapy

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Introduction

Contrast-induced nephropathy (CIN), defined as an acute kidney injury provoked by contrast medium, is a well-described complication of coronary angiography/intervention.[1] Incidence estimates vary from 3.3% to 14.6%, although in very high-risk populations, an incidence of 50% has been described.[2] Risk factors for the development of contrast nephropathy include renal dysfunction, diabetes mellitus, and low mean arterial blood pressure that are pathologic conditions often present in patients affected by heart failure (HF).

As many patients with HF have interventricular conduction delay (QRS > 120 ms), causing mechanical dyssynchrony and inefficient pump function, they undergo to the implantation of cardiac resynchronization therapy (CRT), which is a validated strategy to restore synchronous contraction of left ventricle (LV) through biventricular pacing. Furthermore, CRT improves symptoms, quality of life, and prolongs survival in patients with interventricular conduction delay (QRS complex width > 130 ms), LV ejection fraction (EF) ≤ 35%, and New York Heart Association (NYHA) Class II–IV symptoms.[3] However, up to 30–60%[4] of them do not benefit from this

therapy, and so far, many efforts have been done to find the determinants of this lack of response to CRT, which are related[5–8] to either patients' and procedural characteristics and in addition to the post-procedural management.[9]

Left ventricular lead position is among the predictors of CRT response; however, its procedural placement can be technically challenging as may require a variable amount of contrast medium to visualize the coronary venous system and to target the optimal vessel.

Data regarding CIN after CRT implantation are still scanty, therefore this study sought to elucidate its incidence, the predictors and its impact on CRT response and outcomes.

Methods

Study population

We retrospectively collected data of consecutive HF patients underwent CRT implantation in our institution between November 2012 and September 2017, from the local database. Indication for implantation was given by a consensus of expert cardiologists, the 'Heart Team', according to current European guidelines.[10] Exclusion criteria were age below 18, dialysis, and the lack of complete data regarding renal function. All patients signed the informed consent for the CRT implant and for the collection of personal and clinical data. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethical committee.

Renal function

Diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, spironolactone, and other potentially nephrotoxic agents were routinely withheld based upon the half-life time. The evaluation of renal function was performed at baseline before the CRT implant and after (within 48 hours), by measuring serum levels of creatinine and estimated glomerular filtrate rate (eGFR) with the four-variable Modification of Diet in Renal Diseases equation. The occurrence of CIN within 48 h after CRT implantation was evaluated.

CIN was defined as the increase of at least 0.3 mg/dL of serum creatinine or at least ≥1.5 times baseline value within 48 h, according with Acute Kidney Injury Network (AKIN) classification.[11] According to the severity of serum creatinine increase, the aforementioned classification stages kidney injury as follows: increase from baseline of 1.5 to 1.9 times or ≥0.3 mg/dL (≥26.5 μmol/L) (Stage 1), increase from baseline of 2.0 to 2.9 times (Stage 2), increase of 3.0 times from baseline or increase in serum creatinine of ≥4.0 mg/dL (≥353.6 μmol/L), or initiation of renal replacement therapy or in patients <18 years a decrease in eGFR to <35 mL/min per 1.73 m^2 (Stage 3).

Echocardiography

A standard transthoracic echocardiography was performed in all patients using iE33 Philips system with second-harmonic capability and a 3.5 MHz probe. Electrocardiographically triggered standard 2D grey scale and colour Doppler images were acquired in cine-loop format and transferred to a workstation for offline analysis (EchoPAC 110.0.0; GE Medical Systems, Horten, Norway). Chamber quantification was performed conforming to current recommendations. Left atrium (LA) anteroposterior linear diameter was measured in the 2D left parasternal long-axis view. LV and LA volumes were assessed using Simpson's biplane method and were indexed to body surface area. LV EF was calculated from LV volumes as recommended. Echocardiography was performed at baseline before the CRT implantation and at 6 months by a single operator that was blinded to the occurrence of CIN.

Use of contrast during cardiac resynchronization therapy implantation

Left ventricle lead placement was performed using preshaped guiding sheaths and over the wire leads. Venography was performed to identify the optimal site for LV lead placement. The standard contrast agent used was Iomeron (a tri-iodinated non-ionic monomeric contrast medium, Iomeprol, Bracco). Data regarding the procedure, the device, and the leads implanted were obtained from the local database and confirmed by review of the procedure notes. These included information about the volume of contrast medium used.

Follow-up

Visits were scheduled for each patient at 3, 6, and 12 months, and when not available, telephonic follow-up was performed. After 12 months, the timing for visits was left to the physician's discretion. We evaluated the response to resynchronization therapy, defined as a reduction of LV end-systolic volume (LVESV) of 15% or the increase of five percentage points in EF, and the occurrence of events at follow-up. Clinical events, including cardiac and non-cardiac death, hospitalizations due to a worsening of HF, and non-cardiac hospitalizations, were recorded.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation or median [interquartile range (IQR)] in case of

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non-Gaussian distribution. Categorical variables are expressed as absolute number with percentage (%). Comparison among groups for continuous variables was performed by the Student *t*-test or Mann–Whitney U test (in case of non-Gaussian distribution). Comparison of categorical variables among groups was performed by Chi square test. The Wilcoxon and McNemar tests were used, respectively, to compare continuous and categorical variables before and after CRT. Kaplan–Meier estimate was used to compare survival between CIN and non-CIN patients. Statistical significance is set at a two-tailed probability level of <0.05. All statistical analysis was performed using SPSS software (Version 24.0, IBM, Armonk, NY, US).

Results

Patients' characteristics

Out of 123 patients, 107 were included in the study, whereas 15 were excluded because of incomplete data regarding renal function, and one patient was excluded because already treated with dialysis.

The majority were male patients (79%), with a median age of 71 years (64–78) and a high prevalence of diabetes and coronary artery disease (44% and 59%; *Table 1*). Overall patients at baseline had a mild to moderate impaired renal function (*Table 1*).

Contrast-induced nephropathy and its determinants

Contrast-induced nephropathy occurred in 13 patients (12%) that experienced a significant increase of creatinine and a significant reduction of eGFR compared with baseline (*Table 2*). Twelve out of 13 patients experienced a Stage 1 injury, and only one patient experienced a Stage 2. The volume of contrast medium used for the venography was 16 mL (16–24) with a trend towards higher volume in no-CIN patients. Beyond a high serum creatinine, none of the baseline clinical characteristics and neither the echocardiographic nor the laboratory variables at baseline were associated with the occurrence of CIN (*Table 1*).

Table 2 Renal function at baseline and after cardiac resynchronization therapy implantation

Variables	baseline	Post-CRT	*P* value
Creatinine, mg/dL			
• Overall	1.2[0.9–1.7]	1.2[0.9–1.6]	0.6
• No-CIN	1.1[0.9–1.7]	1.2[0.9–1.5]	0.03
• CIN	1.3[1.2–1.7]	1.9[1.6–2.9]	0.001
eGFR, mL/min			
• Overall	63[40–83]	63[41–82]	0.9
• No-CIN	66[40–82]	65[46–86]	0.03
• CIN	47[44–74]	36[22–45]	0.002

CIN, contrast-induced nephropathy; CRT, cardiac resynchronization therapy; Crea, creatinine; eGFR, estimated glomerular filtrate rate.

Table 1 Baseline characteristics

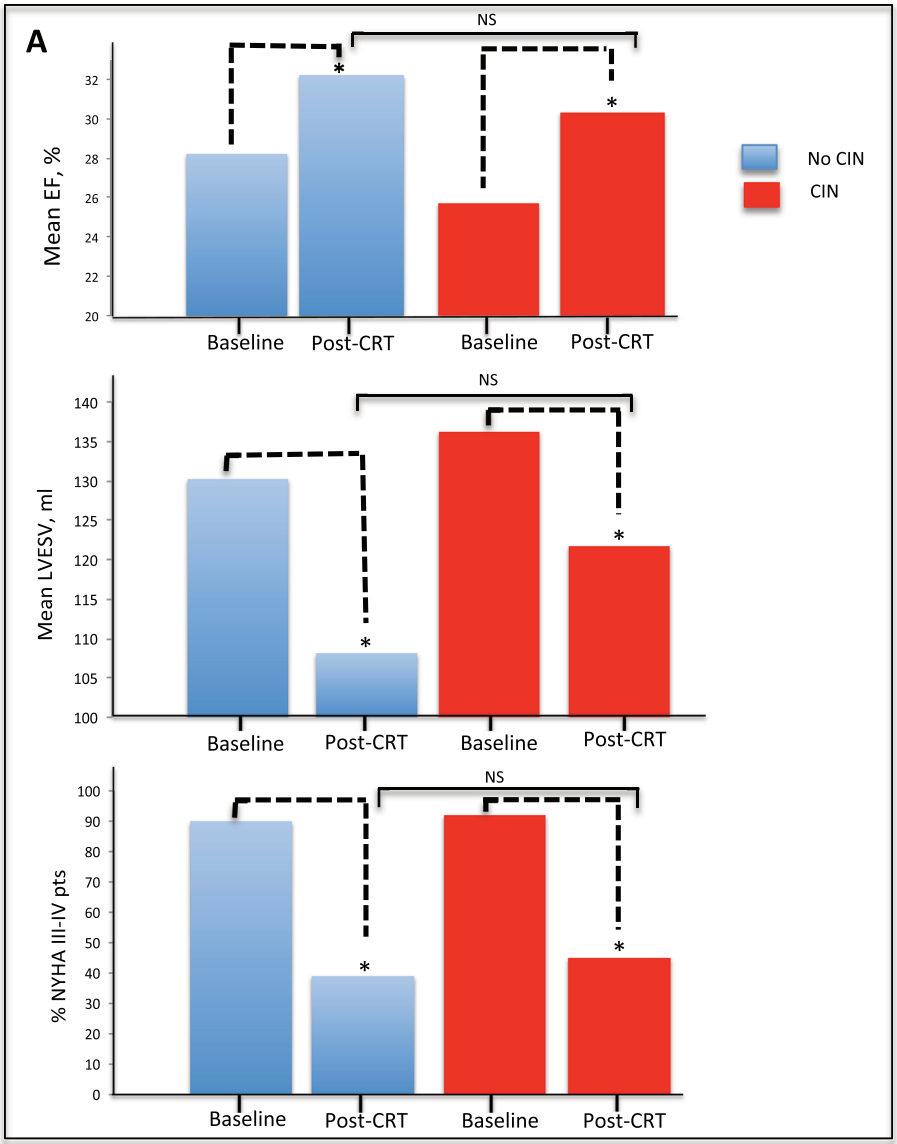
Variables	Overall (107)	No-CIN (94)	CIN (13)	*P* value
Males, (%)	85/107 (79)	77/94(82)	8/13(62)	0.1
Age, yrs	71[64–78]	71[64–78]	73[64–81]	0.4
Hypertension, (%)	74/106 (70)	64/93 (69)	10/13(77)	0.8
Dyslipidemia, (%)	51/106 (48)	44/93(47)	7/13(54)	0.8
BMI, kg/m^2	27.9 ± 5.3	27.8 ± 5.4	28.8 ± 5.6	0.6
Diabetes, (%)	45/106(44)	39/90(43)	6/13(46)	1
COPD, (%)	41/106(39)	33/93(36)	8/13(62)	0.1
CAD, (%)	63/106(59)	56/93(60)	7/13(54)	0.8
I-CMP, (%)	44/107(41)	38/94(40)	6/13(46)	0.8
Prior AMI, (%)	56/106(53)	49/93(53)	7/13(54)	1
PCI, (%)	53/106(50)	46/93(50)	7/13(54)	1
CABG, (%)	22/106(21)	17/93(18)	5/13(39)	0.1
NYHA III/IV, (%)	94/105(90)	84/93(90)	11/12(92)	0.7
QRS, ms	158 [146–160]	160[146–160]	150[148–166]	0.6
LBBB, (%)	77/104(74)	66/91(73)	11/13(85)	0.5
RBBB, (%)	19/104(18)	18/91(20)	1/13(8)	0.5
AF, (%)	31/106(29)	26/93(28)	5/13(39)	0.5
EF, %	28[23–32]	29[23–33]	26[22–29]	0.1
LVESV, ml	128[95–152]	126[92–150]	137[122–157]	0.4
Upgrade, (%)	31/107(29)	27/94(29)	4/13(31)	1
Crea, mg/dl	1.2[0.9–1.7]	1.1[0.9–1.7]	1.3[1.2–1.7]	0.04
eGFR, ml/min	63[40–83]	66[40–82]	47[44–74]	0.1
Contrast, ml	16[16–24]	24[16–30]	16[16–16]	0.07

AF, atrial fibrillation; AMI, acute myocardial infarction; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; Crea, creatinine; eGFR, estimated glomerular filtrate rate; EF, ejection fraction; I-CMP, idiopathic cardiomyopathy; LBBB, left bundle branch block; LVESV, left ventricle end-systolic volume; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RBBB, right bundle branch block; TAPSE, tricuspid annular plane systolic excursion.

Clinical and echocardiographic response to cardiac resynchronization therapy

Echocardiographic data at 6 months were available in 63 (59%) patients (*Figure 1*). After CRT, the EF significantly increased in parallel with a significant decrease of LVESV (Panel A, *Figure 1*), in both CIN and no-CIN patients, and likewise, the magnitude of variation from baseline (delta, Δ) was not different between groups (Panel B, *Figure 1*). Furthermore, at 6 months, mean EF and mean

Figure 1 Response to cardiac resynchronization therapy after 6 months. Panel A: Echocardiographic response and functional class at baseline and 6 months after cardiac resynchronization therapy implant in no contrast-induced nephropathy and contrast-induced nephropathy patients. Panel B: The magnitude of variation from baseline is represented by the Δ (6 months value-baseline value). CIN, contrast-induced nephropathy; CRT, cardiac resynchronization therapy; EF, ejection fraction; LVESV, left ventricle end-systolic volume; NYHA, New York Heart Association class.



B	*No CIN*	*CIN*	*p*
ΔEF, %	3.3±6.4	2.7±4.4	0.8
ΔLVESV, ml	-17.4±38	-33.6±41	0.3
ΔNYHA III-IV, %	51	46	0.8

LVESV were not significantly different between no-CIN and CIN [29 (23–33) vs. 26 (22–29), *P* = 0.1; 126 (92–150) vs. 137 (122–157), *P* = 0.4] (Panel A, *Figure 1*). Overall, 36/63 patients (57%) were considered responders, 29/53 (55) in the no-CIN group, and 7/10 (70) in the CIN group (*P* = 0.3). Baseline characteristics of responders and non-responders in the overall population, in the no-CIN group, and in the CIN group are reported in Supporting Information, *Tables S1*, *S2*, and *S3*.

Of note, when considering only patients responders to CRT, those with CIN had significant lower EF at 6 months (*Figure 2*), and also, LVESV was higher although not significantly [107 (91–112 IQR) vs. 84 (72–105 IQR), *P* = 0.16].In these patients none of the baseline characteristics was associated with the occurrence of CIN (Table S4).

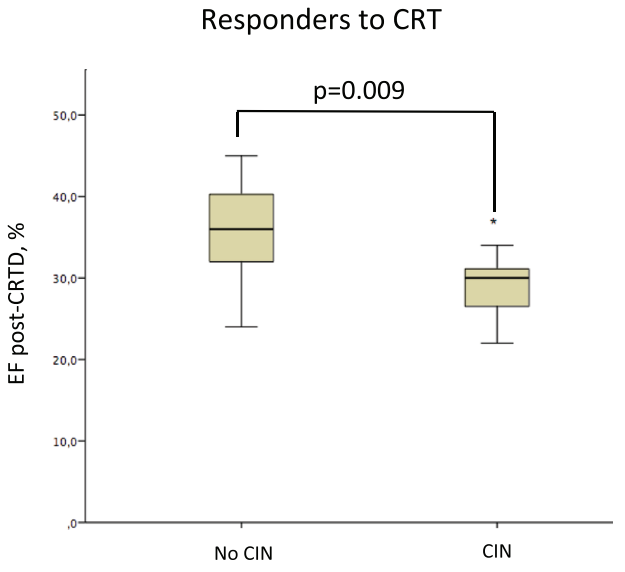
Data regarding functional class were available for 77 patients. Patients in class NYHA III/IV were significantly less after CRT implantation in both CIN and no-CIN groups. Furthermore, the occurrence of CIN did not affect functional improvement as the number of patients still in class NYHA III–IV after CRT was not significantly different between groups (*Figure 1*).

Clinical outcomes

The median clinical follow-up was of 112 weeks (59–160) and was available for 88 patients (82%). Of these, 38 patients (43%) experienced a clinical event: 19 (22) patients underwent a new hospitalization (11 due to worsening of HF and 8 due to non-cardiac causes), 18 (20) died (16 cardiac death and 2 non-cardiac death), and 1 (1) patient after a non-HF-related hospitalization died of non-cardiac death. No significant differences were found in the incidence of clinical events between CIN and no-CIN patients (*Table 3*), and likewise, the survival was not significantly different (69% vs. 80%, *P* = 0.2) (*Figure 3*, Panel A). *3*

Responders to CRT had better survival than non-responders (90% vs. 72%, *P* = 0.07) (*Figure 3*, Panel B) albeit among responders the survival in those who experienced CIN was lower than in no-CIN patients (71% vs. 93%, *P* = 0.035) (*Figure 3*, Panel C).Likewise, the mortality rate was lower in responders compared with nonresponders(11% vs. 27%; P = 0.17); nonetheless, those who experienced CIN among responders had a higher mortality(29%) similar to those who did not respond to CRT(Figure 3, Panel D).

Figure 2 Ejection fraction at 6 months after cardiac resynchronization therapy in the responders group. CIN, contrast-induced nephropathy; CRT, cardiac resynchronization therapy; EF, ejection fraction.



Discussion

Main findings

1 Twelve percent of patients undergoing CRT implantation experience CIN. None of the baseline clinical, echocardiographic, or laboratory variables is associated with CIN except for a high serum creatinineat baseline.
2 In the overall population, CIN does not affect the clinical and echocardiographic response to CRT, and, remarkably, patients with CIN do not experience more cardiovascular events or lower survival than patients without.
3 Among responders to CRT, those with CIN have a significant lower EF recovery and a significant lower survival compared with those withoutCIN.

Contrast-induced nephropathy and cardiac resynchronization therapy

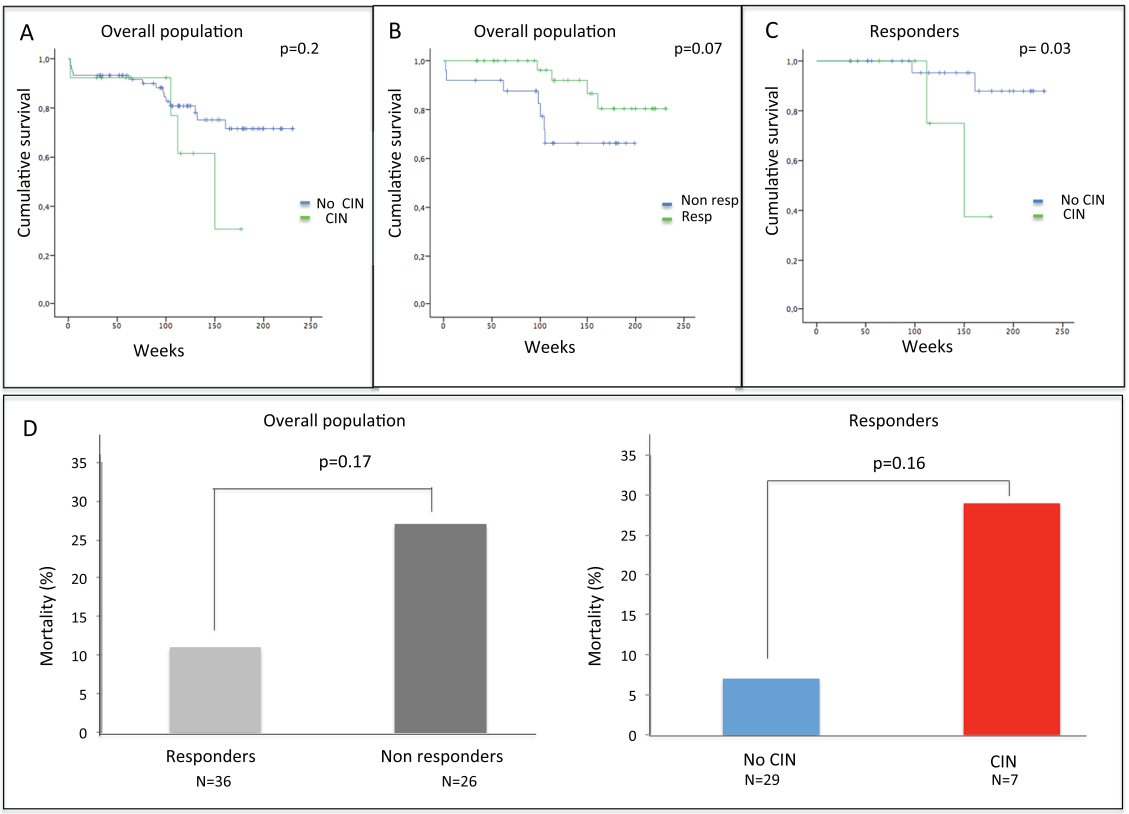
Cardiac resynchronization therapy efficacy depends on LV lead positioning that ideally should be placed in a lateral or postero-lateral branch of coronary sinus to diminish the

Table 3 Clinical events

Clinical events	No-CIN	CIN	*P* value
HF hosp, (%)	11/75(15)	0/13(0)	0.4
Non HF hosp, (%)	7/75(9)	2/13(15)	0.6
Death (%)	15/75(20)	4/13(31)	0.5
Cardiac death, (%)	13/75 (17)	3/13(23)	0.7
Non-cardiac death, (%)	2/75(3)	1/13(8)	0.4
Overall events,(%)	33/75(44)	5*/13(38)	1

CIN, contrast-induced nephropathy; HF, heart failure.
*1 patient experienced both non-heart failure (HF)-related hospitalization and non-cardiac death.

Figure 3 Kaplan–Meier curves and mortality rate in the overall population and in the responders group. CIN, contrast-induced nephropathy.



dyssynchrony between lateral and septal walls. Balloon-occlusive contrast angiography of the coronary sinus tributaries is therefore recommended to guide electrode positioning.

Nonetheless, coronary sinus cannulation and angiography can still be challenging, and several injections of contrast medium might be necessary. Iodinated contrast causes direct cellular injury to kidney tubular cells that undergo swelling, blebbing, and apoptosis [12] resulting in contrast nephropathy. As reported by Tester *et al.*, the worsening of renal function is proportional to the amount of contrast used.[13]

In our study, the median amount of contrast used was low (16 mL) as the majority of LV lead were quadripolar. The advent of these new leads rendered easier to find the optimal pacing site, as they can pace the LV wall at several locations and with multiple vectors.[14]

Although the amount of contrast used was low, the incidence of CIN was 12% that is in line with data of Cowburn (14%)[15] and Kowalczyk (10.2%).[16] Tester *et al.*[7] reported for the same amount of contrast lower incidence; however, differently from us, they considered the increase of Creatinine ≥48 h and not within.

Contrast-induced nephropathy and clinical and echocardiographic response to cardiac resynchronization therapy

According to previous studies, we report that the rate of responders in the CIN group is similar to that in the no-CIN group. Furthermore, we found that after CRT the rate of patients in NYHA class III/IV, EF, and LVESV are not significantly different between groups.

Interestingly, among patients responders to CRT, those with CIN had a significant lower recovery of EF, suggesting that factors other than CIN play a major role in determining response to CRT, but still, CIN can influence recovery of EF and survival. This can be explained by the tight relation between renal and cardiac function, indeed as the reduction of cardiac output impairs renal function, also a renal damage can lead to worsening of cardiac performance. For instance, as reported by Bagshaw *et al.*, the cardio-renal syndrome Type 3 is characterized by the occurrence of an acute kidney injury that precipitates and contributes to the development of acute cardiac injury.[17] In this circumstance, inflammatory cytokines as tumour necrosis factor-alpha and interleukin-6 have been shown to have direct cardio-depressant effects

characterized by reduced LV fractional shortening and elevated LV end-diastolic and systolic dimensions.

We can therefore speculate that during CIN the same factors may be involved in the reduced recovery of EF in responders.

Contrast-induced nephropathy and clinical outcomes

Kowalczyk *et al*. analysed outcomes of CIN after CRT reporting a mortality rate of 50% in patients with CIN, that was significantly higher compared with no-CIN.[16] In our study, we found a lower mortality rate (31%) that was not significantly different from that of no-CIN patients. Probably, this discrepancy is because of the differences in baseline and procedural characteristics. In the study of Kowalczyk *et al.,* indeed, patients' EF at baseline was lower and the LVESV was higher compared to our population, and furthermore, the volume of contrast medium used was higher. As the worsening of renal function is proportional to the amount of contrast used[7] and in our study, we used a very small amount of contrast(12 out of 13 patients experiencing a CIN Stage 1 and only 1 patient experiencing a Stage 2) therefore, this can partially explain the low mortality rate that we found.

Furthermore, we report that responders' survival is 90% at a median follow up of 112 weeks; however, in those responders with CIN, the survival markedly decreased to 71%, which is similar to that of non-responders (72%) (*Figure 3*), suggesting that the beneficial effect of responding to CRT is nullified if CIN occurs. Although these results need to be further confirmed in larger populations, these survival rates may be driven by the lower EF recovery; indeed, Breathett *et al*.[18] previously demonstrated that changes in EF (assessed by radionuclide ventriculography) predicted survival and hospitalization in a large cohort of HF patients with reduced EF. However, the very limited number of patients with CIN and not responding to CRT in our study does not allow us to understand the actual survival rate in these patients that could likely be worse than what we found in responder patients.

Conclusions

The incidence of CIN in patients undergoing CRT implantation is rather high. CIN does not influence response to CRT overall, howeveramong responders impairs the recovery of EF and survival. Further studies are needed to validate these results in a larger population.

Limitations

Our study, due to its retrospective nature, has important limitations that need to be highlighted:

(1) The volume of contrast used for the implantation was relatively small so is it possible that higher amounts would be associated with higher incidence of CIN and different outcomes.
(2) Data regarding echocardiographic response and outcomes are not available for all patients included in the study, as many of them were referred from other physicians, and for logistic reasons, they were not followed in our institution, or they were not reachable by phone calls.
(3) Data regarding the adequacy of lead placement were not available, so we cannot exclude that the difference in EF between CIN and no-CIN patients in the responders group is linked to a better positioning of LV lead in no-CIN group, although this seems unlikely because both groups responded similarly to resynchronization.
(4) Creatinine and eGFR values after discharge were not available at follow-up; therefore the worse outcome of CIN patients responders to CRT might be explained also by a worse renal function.
(5) The small number of patients in the study is a major limitation. Although we found a significant lower survival in responders with CIN, further studies are needed to confirm these data in a larger population.

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Conflict of interest

None.

Funding

None.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Cardiac magnetic resonance imaging.
Table S1. Baseline and procedural characteristicsin responders and non responders.
Table S2. Baseline and procedural characteristics in the no-CIN group.
Table S3. Baseline and procedural characteristics in the CIN group.
Table S4. Baseline and procedural characteristics in the group of responders.

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