ORIGINAL RESEARCH ARTICLE

Transcatheter indirect mitral annuloplasty induces annular and left atrial remodelling in secondary mitral regurgitation

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Abstract

Aims   Mitral annuloplasty using the Carillon Mitral Contour System (CMCS) reduces secondary mitral regurgitation (SMR) and leads to reverse left ventricular remodelling. The aim of this study was to evaluate the effect of the CMCS on the mitral valve annulus (MA) and left atrial volume (LAV).

Methods and results   We retrospectively evaluated the data of all patients treated with the CMCS at our centre. Using trans-thoracic echocardiography, MA diameters were assessed by measuring the anterolateral to posteromedial extend (ALPM) and the anterior to posterior (AP) dimensions, respectively. Also, LAV and left ventricular end-diastolic volume (LVEDV) were assessed. Patients were examined at three time points: baseline, at 20–60 days (30dFUP), and at 9–15 months (1yFUP), using paired analysis. From July 2014 until March 2019, 75 cases of severe SMR were treated using CMCS. Cases in which other devices were used in combination (COMBO therapy, *n* = 35) or in which the device could not be implanted (implant failure, *n* = 3) were excluded, leaving 37 patients in the present analysis. Analysis at 30dFUP showed a significant reduction of 16% in the mean ALPM diameter (7.27 ± 5.40 mm) and 15% in the AP diameter (6.57 ± 5.33 mm). Analysis of LAV also showed a significant reduction of 21% (36.61 ± 82.67 mL), with no significant change in LVEDV. At 1yFUP, the reduction of both the mean ALPM diameter of 14% (6.24 ± 5.70 mm) and the mean AP diameter of 12% (5.46 ± 4.99 mm) remained significant and stable. The reduction in LAV was also maintained at 23% (37.03 ± 56.91 mL). LAV index was significantly reduced by 17% at 30dFUP (15.44 ± 40.98 mL/m^2) and by 13% at 1yFUP (11.56 ± 31.87 mL/m^2), respectively. LVEDV index showed no significant change at 30dFUP and a non-significant 10% reduction at 1yFUP (17.75 ± 58.79 mL/m^2).

Conclusions   The CMCS successfully treats symptomatic SMR with a stable reduction of not only the AP diameter of the MA, but the current study also demonstrates an additional reduction of the ALPM dimension at both 30dFUP and 1yFUP. We have also shown for the first time that LAV and LAV index are significantly reduced at both 30dFUP and 1yFUP and a non-significant positive remodelling of the LVEDV. This positive left atrial remodelling has not been looked for and demonstrated in earlier randomized studies of CMCS.

Introduction

Secondary mitral regurgitation (SMR) is prevalent in patients with chronic heart failure, increasing mortality and morbidity.[1–4] Percutaneous mitral valve repair has become a sound alternative to cardiac surgery in high-risk patients with severe mitral regurgitation,[5,6] with one recent edge-to-edge therapy recently associated with a reduction of mortality following successful treatment.[7]

One of the components of SMR is dilation of the mitral valve annulus (MA) and increased left atrial volume (LAV).[8] The Carillon Mitral Contour System® (CMCS; Cardiac Dimensions, Inc., Kirkland, WA, USA) is the only device having CE approval to treat mitral regurgitation by addressing MA dilation through indirect annuloplasty, utilizing the proximity of the coronary sinus (CS) to the MA. Several studies have shown the safety and efficacy of the device with reduction in mitral regurgitation grade and improvement in exercise capacity, quality of life,[9–11] and left ventricular (LV) reverse remodelling.[11,12] The device also reduces MA dilation, but there are no data on the treatment effect on left atrial (LA) enlargement. LA enlargement, however, is associated with a heightened risk of cardiovascular events and mortality.[13,14]

In this study, we sought to elucidate the effect of CMCS therapy on MA dimensions, LV end-diastolic volume (LVEDV), and LAV.

Methods

Study population

We retrospectively evaluated the data of all patients treated with the CMCS system (n = 75). All patients were treated for symptomatic mitral regurgitation ≥2+ and were not eligible for cardiac surgery as assessed by the heart team. Therapy strategy was either CMCS alone (MONO, n = 40) or a combination therapy (COMBO, n = 35), either adding edge-to-edge therapy, that is, MitraClip® (MC; Abbott Vascular, Santa Clara, CA, USA) or NeoChord (NeoChord, Inc., St. Louis Park, MN, USA). The present analysis focuses on those patients treated with the CMCS only (MONO) (*Figure 1*). The study was approved by the local ethics committee (2019-14692).

Percutaneous mitral valve repair

The details of the procedure have been reported previously.[15,16] In short, under fluoroscopic guidance, the delivery catheter was advanced to the right atrium via the right internal jugular vein. Anchor size and device length were determined by measuring the CS, opacified by direct CS contrast injection (*Figure 2A*). To implant the device, the distal anchor is placed at a suitable location, following which tension on the MA is achieved by pulling the delivery system by 4 to 6 cm. Finally, after confirming no impingement of either the circumflex artery or the right coronary artery by selective arteriography, the device is locked in position by deploying the proximal anchor (*Figure 2B*) and released. All patients were placed under general anaesthesia. Following the procedure, patients were monitored for at least 24 h.

Echocardiography

Using transthoracic echocardiography, MA was assessed by measuring the anterolateral to posteromedial extend (ALPM) in the apical two-chamber view and the anterior to posterior (AP) dimension in the apical three-chamber view, respectively. LAV and LVEDV were measured using the biplane approach in the apical four-chamber and two-chamber views, respectively (*Figure 3*). Measurements were taken during end-diastole. Indices were calculated using the formula described by Mosteller.[17] The ultrasound machines used were Philips iE33 and Epiq 7C (Philips, Andover, MA, USA) and GE Vivid E95 (GE Healthcare, Chicago, IL, USA), and analysis was conducted using IntelliSpace Cardiovascular and QLAB (Philips). Measurements were taken pre-procedure (baseline), at 20–60 days (30dFUP), and at 9–15 months (1yFUP).
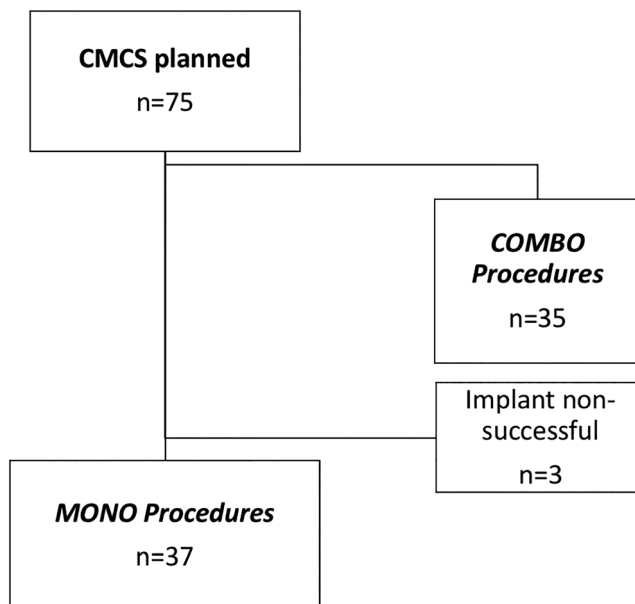
Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics Version 23 (IBM Corp., Armonk, NY, USA). The Kolmogorov–Smirnov test was used to test for normality following which Student's t test was performed on normally distributed data, while the Wilcoxon test was used for non-normally distributed data. P-values smaller than 0.05 were considered significant. Figures were created using IBM SPSS Statistics Version 23 and Microsoft Excel 16.9 (Microsoft, Redmond, WA, USA).

Results

Patient characteristics

From July 2014 until March 2018, 75 patients underwent treatment for mitral regurgitation, using CMCS. Of these, 72 were successfully implanted, with the MONO approach used in 37, all in SMR. Demographical and echocardiographic data are depicted in *Tables 1* and *2*, respectively. Follow-up rate at 30dFUP was 86% (n = 32) and at 1YFUP was 56% (n = 21), respectively. Results are shown in *Figures 4* and *5* and *Table 3*.

Figure 1 Patient selection and grouping. COMBO, either CMCS and MC® or CMCS and NeoChord® were both implanted, respectively; MONO, only CMCS was implanted.

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        ┌──────────────────┐
        │   CMCS planned   │
        │      n=75        │
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        ┌────────┴─────────┐
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        │         ┌──────────────────┐
        │         │      COMBO       │
        │         │   Procedures     │
        │         │      n=35        │
        │         └──────────────────┘
        │              ┌──────────────────┐
        │              │  Implant non-    │
        │              │   successful     │
        │              │      n=3         │
        │              └──────────────────┘
┌──────────────────┐
│ MONO Procedures  │
│      n=37        │
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Figure 2 Sizing and placement of CMCS: (A) venogram of CS for sizing of CMCS and parallel coronary angiogram, visualizing the right circumflex coronary artery, unobstructed by the CMCS device; (B) placement of proximal anchor; (C) cinching of CMCS and parallel visualization of right circumflex coronary artery; and (D) final placement.
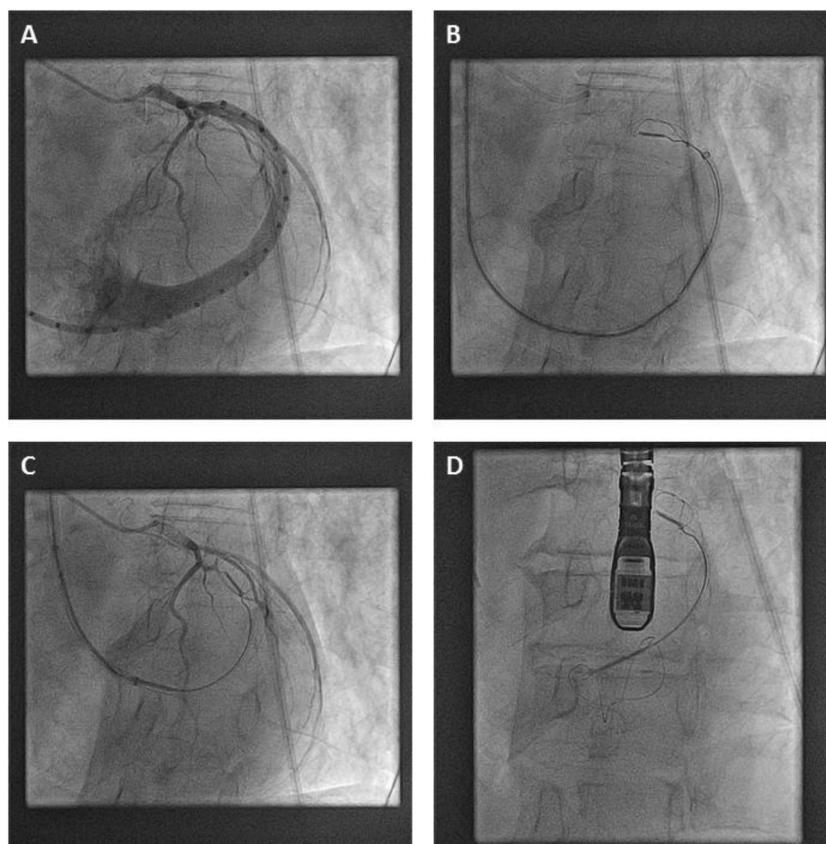
Figure 3 Echocardiography—baseline (top row) vs. 1 year follow-up (bottom row): assessment of biplane left atrial volume in four-chamber view (A, D) and apical two-chamber view (B, E) and measurement of mitral valve area diameters in the apical two-chamber view (anterolateral to posteromedial extend, B, E) and the apical three-chamber view (anterior to posterior, C, F). In this example, left atrial volume is reduced by approximately 26% (190 vs. 140 mL), while anterolateral to posteromedial extend decreased by 23% (46 vs. 35 mm) and AP 30% (39 vs. 27 mm), respectively.
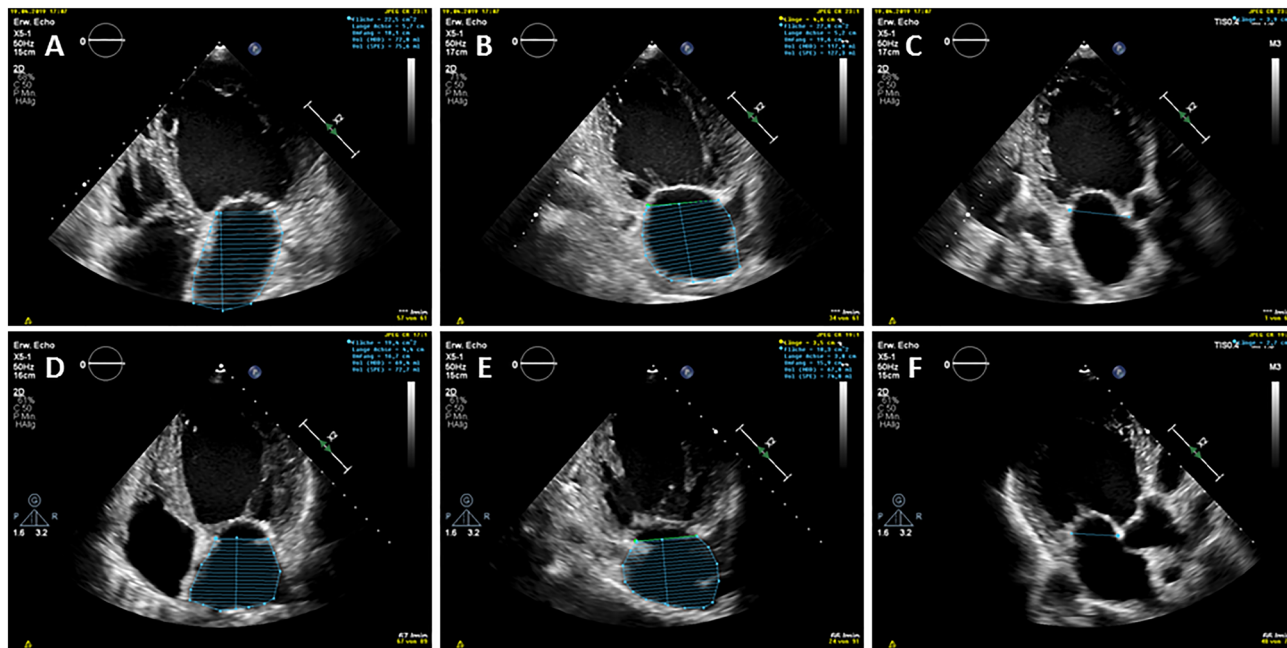
Annulus diameter

Analysing data at the 30dFUP, there was a significant reduction of 16.0% in the mean ALPM diameter [n = 32, from 43.53 ± 3.82 to 36.25 ± 3.71 mm, a mean reduction of 7.28 ± 5.40 mm, confidence interval (CI) 5.32 to 9.22; $P < 0.001$], as well as a 15.0% reduction in the AP diameter (n = 32, from 41.56 ± 4.53 to 34.99 ± 5.47 mm, a mean reduction of 6.57 ± 5.33 mm, CI 4.65 to 8.49; $P < 0.001$). At the 1yFUP, there was a persistently significant 14% reduction of the mean ALPM diameter (n = 21, from 43.81 ± 3.94 to 37.57 ± 5.23 mm, a reduction of 6.24 ± 5.70 mm, CI 3.64 to 8.83; $P < 0.001$). The reduction of the mean AP diameter remained at 12% (from 42.41 ± 3.45 to 36.95 ± 5.83 mm, n = 21, a reduction of 5.46 ± 4.99 mm, CI 3.19 to 7.73; $P < 0.001$).

There were no statistical differences of ALPM and AP diameters in between 30dFUP and 1yFUP, respectively (data not shown).

Left ventricular and left atrial volumes

Analysis of LAV at 30dFUP showed a significant reduction of 21% [n = 32, -36.61 ± 82.67 mL, CI 6.81 to 66.41 (169.96 ± 129.76 vs. 133.35 ± 65.68); $P = 0.018$]. With 23%, reduction of LAV remained statistically significant at 1yFUP

[n = 21, −37.03 ± 56.91 mL, CI 11.13 to 62.94 (157.60 ± 73.22 vs. 120.57 ± 48.89); $P = 0.007$]. LAV index (LAVi) was also significantly reduced at 30dFUP by 17% [-15.44 ± 40.98 mL/m^2, CI 3.27 to 27.60 (90.08 ± 65.02 vs. 74.64 ± 36.65); $P = 0.014$] and at 1yFUP by 13% [-11.56 ± 31.87 mL/m^2, CI 0.26 to 22.86 (83.68 ± 39.93 vs. 72.12 ± 37.28); $P = 0.045$], respectively.

Concerning LVEDV, there were no statistically relevant reductions at 30dFUP [n = 32, −4.31 ± 52.33 (175.55 ± 91.45 vs. 171.23 ± 77.81); $P = 0.644$] nor at 1yFUP [n = 21, −13.72 ± 58.42 (176.99 ± 104.24 vs. 163.27 ± 92.53); $P = 0.295$], respectively. Also, we did not observe a significant change in LVEDV index (LVEDVi) at 30dFUP [−0.50 ± 48.10 mL/m^2, CI −14.32 to 13.32 (177.05 ± 84.93 vs. 177.55 ± 78.75); $P = 0.942$]. At the 1yFUP, there was a 10% reduction, showing a tendency but not reaching statistical significance [-17.75 ± 58.79 mL/m^2, CI −2.15 to 37.64 (171.15 ± 88.44 vs. 153.40 ± 88.43), $P = 0.079$] (*Figure 6*).

There were no statistical differences of LAV, LAVi, LVEDV, and LVEDVi in between 30dFUP and 1yFUP, respectively (data not shown).

Discussion

This is the first study to evaluate the positive remodelling effect of the CMCS on both MA diameters, that is, AP

Table 1 Baseline demographics

Sex	37
Male	20 (54%)
Female	17 (46%)
Age at procedure (years)	71.08 ± 11.09
Height (cm)	161.67 ± 0.40
Weight (kg)	76.03 ± 28.36
BMI (kg/m^2)	26.10 ± 8.93
BSA (m^2)	1.90 ± 0.26
Logarithmic EuroSCORE	20.28
Arterial hypertension	28 (75%)
Hyperlipoproteinaemia	35 (94%)
Pulmonary hypertension	21 (56%)
Coronary artery disease	28 (75%)
PCI	25 (67%)
CABG	1 (2%)
Previous myocardial infarction	21 (56%)
Type of cardiomyopathy	
DCM	12 (32%)
ICM	21 (56%)
LACM	4 (10%)
Stroke	5 (13%)
Peripheral artery disease	9 (24%)
Atrial fibrillation	21 (56%)
PM or ICD	10 (27%)
Diabetes mellitus	9 (24%)
Chronic pulmonary disease	8 (21%)
Chronic renal failure	7 (18%)
Dialysis	2 (5%)
Previous valve replacement	10 (27%)
SAVR	5 (13%)
TAVR	5 (13%)
Medication	
Anti-platelets	24 (64%)
Oral anticoagulation	21 (56%)
ACEI or ARB	28 (75%)
Beta-blockers	28 (75%)
Digitalis	4 (10%)
Loop diuretics	29 (78%)
Spironolcatone	14 (37%)
Statin	18 (48%)
NYHA class	
II	7 (18%)
III	19 (51%)
IV	3 (8%)
LVEF	35.29 ± 13.17%
Grade of mitral regurgitation	
2+	3 (8%)
3+	31 (84%)
4+	3 (8%)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BSA, body surface area; CABG, coronary artery bypass graft; DCM, dilated cardiomyopathy; ICD, implantable cardioverter/defibrillator; ICM, ischaemic cardiomyopathy; LACM, left atrial cardiomyopathy; LVEF, left ventricular ejection fraction, the standard deviation is shown; NYHA, New York Health Association; PCI, percutaneous coronary intervention; PM, pacemaker; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.
Continuous variables are shown as mean ± standard deviation and categorical variables as number (%). Pulmonary hypertension is defined as a systolic pulmonary artery pressure of >55 mmHg as assessed by echocardiography. Anti-platelets included aspirin, clopidogrel, prasugrel, or ticagrelor or a combination of these.

Table 2 Baseline echo characteristics

	Overall
Baseline—all	$n = 37$
ALPM (mm)	43.24 ±4.13
AP (mm)	41.77 ±4.38
LAV (mL)	175.20 ±127.05
LVEDV (mL)	177.59 ±90.32
Baseline (30 day follow-up visitors)	$n = 32$
ALPM (mm)	43.53 ± 3.82
AP (mm)	41.56 ± 4.53
LAV (mL)	169.96 ± 129.76
LAVi (mL/m^2)	90.08
LVEDV (mL)	175.54 ± 91.45
LVEDVi (mL/m^2)	177.05 ± 84.93
Baseline (1 year follow-up visitors)	$n = 21$
ALPM (mm)	43.80 ± 3.94
AP (mm)	42.41 ± 3.45
LAV (mL)	157.60 ± 73.22
LAVi (mL/m^2)	83.68 ± 39.93
LVEDV (mL)	176.99 ± 92.53
LVEDVi (mL/m^2)	171.14 ± 88.44

ALPM, anterolateral to posteromedial extend; AP, anterior to posterior; LAV, left atrial volume; LAVi, left atrial volume index; LVEDV, left ventricular end-diastolic volume; LVEDVi, left ventricular end-diastolic volume index.
Continuous variables are shown as mean ± standard deviation and categorical variables as number (%).

and ALPM, and LAV as well as LAVi in a large, single-centre cohort of 37 patients suffering from symptomatic severe SMR.

Dilation of the MA is a typical finding in SMR.[3,18] A characteristic anatomic feature is loss of the saddle shape of the MA, thus increasing leaflet stress contributing to malcoaptation.[19]

Reduction of MA diameter by ~15% using the CMCS has already been demonstrated in the TITAN studies.[10,11] Our results confirm those findings, showing a reduction of AP by 15% at 30dFUP and 12% at 1yFUP, respectively. However, in this study, we also observed a persistent reduction in the perpendicular ALPM dimension at 30dFUP and at 1yFUP. A change in the AP diameter has also already been shown in other transcatheter techniques. For instance, in the context of edge-to-edge leaflet therapy in SMR, one study evaluating the immediate effect of the therapy on mitral valve geometrics demonstrated a significant reduction in the AP diameter, although here too, the ALPM dimensions were not improved.[20]

Our observation of additional reduction of the ALPM diameter is novel and not in contrast with these findings. In edge-to-edge therapy, change of the AP diameter alone is not surprising, as the reductive force of the therapy is directed in this direction only. To have the greatest effect in indirect annuloplasty using the Carillon system, the distal anchor is deployed as deep into the CS as possible, in order to encircle the greatest possible proportion of the mitral annulus from the left to right trigone. Hence, the cinching force is executed not only in the AP dimension but also in the ALPM plane. In the TITAN-II-study, for instance, as AP was thought to be most impacted by SMR, only the AP diameter (not ALPM) was assessed.[11]

Left atrial remodelling, incorporating changes of atrial geometric structure and haemodynamic function, is the result

Figure 4 Evolution of mitral valve annulus: dimensions of anterior to posterior (AP) (top row) and anterolateral to posteromedial extend (ALPM) (bottom row) as demonstrated by boxplot (A, C) and direct comparison (B, D).
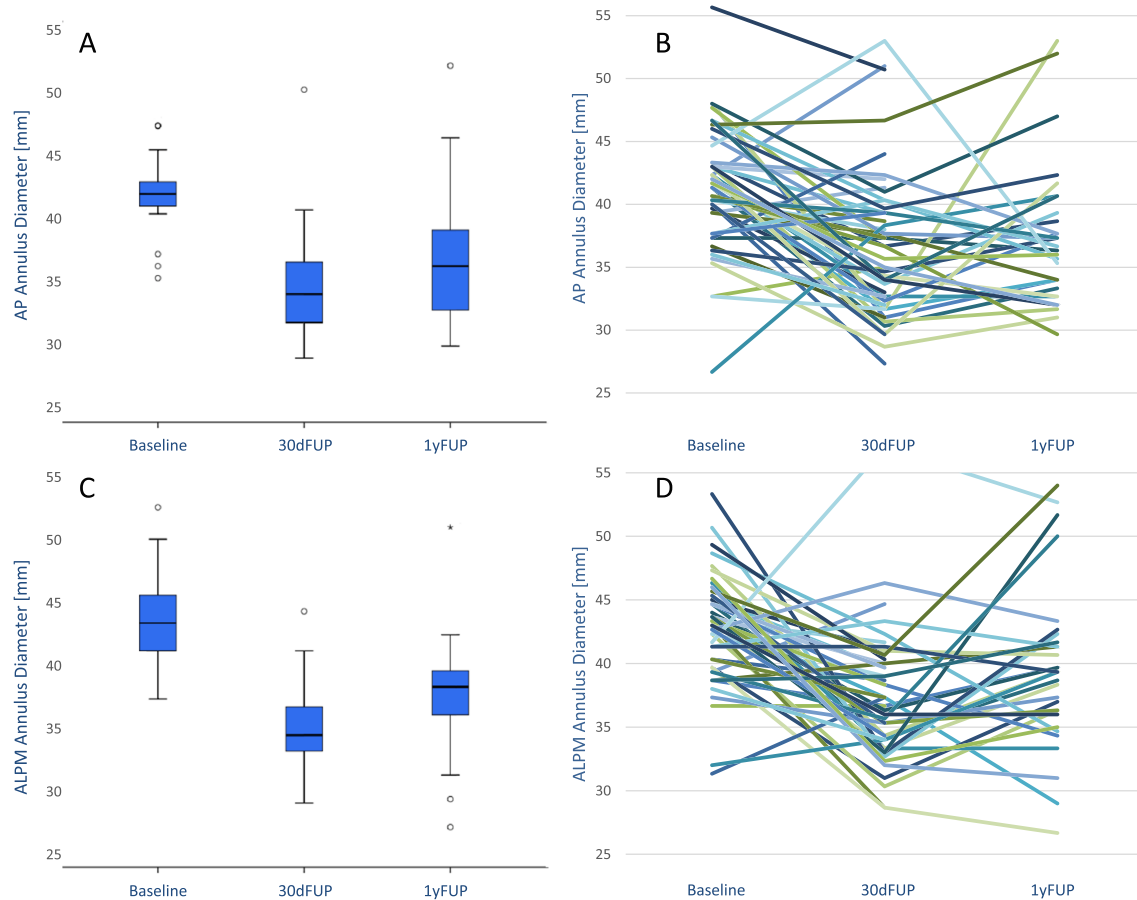
of the combined stress forces on the LA wall including those due to increased LV end-diastolic pressure, atrial arrhythmias, and mitral annulus deformation or strain as well as valve dysfunction[21] and is also influenced by activation of the renin–angiotensin–aldosterone system, depletion of atrial natriuretic peptide, and increased LA pressure.[22] These combined effects lead not only to impaired LA systolic function and diastolic compliance, and electric conduction abnormalities, but also to changes in the molecular structure[21,23] prompting the term atrial cardiomyopathy.[24] Therefore, the drivers of LA remodelling mirror those of LV remodelling as seen in heart failure. LA remodelling is associated with a heightened risk of cardiovascular events and mortality.[13] In this study, we have demonstrated a significant decrease of LAV, both as absolute measurements and as indexed to body surface area (LAVi). The remodelling starts as early as 30 days after the procedure and the decrease remains stable at 1yFUP.[25,26]

This effect of the Carillon device on LV remodelling with a reduction of LVEDV of 10.42 mL in our series has recently been confirmed in the larger and randomized REDUCE FMR study.[11,12,27] Our data, with similar baseline

LV volumes as well as the LVEDVi, demonstrate a similar reduction at 1 year, suggesting that the lack of statistical significance in our data is likely due to an insufficient patient cohort size.

The 'reverse LA remodelling' that we demonstrated in this study could represent a novel marker of beneficial changes in halting progressive LA dilatation as a syndrome and consequence of heart failure, possibly preceding in time the reverse remodelling of the LV demonstrated as a significant benefit of Carillon Mitral Contour System in the randomized REDUCE FMR trial.[27]

Limitations

The present dataset should be viewed in the light of its retrospective nature and single-centre origin, and hidden confounders cannot be accounted for.[28] However, each operator followed standard procedural guidance, and the echocardiograms were performed by operators disconnected with the device procedure and analysed in a blinded fashion. Nevertheless, the data are hypothesis generating rather than

Figure 5 Evolution of left atrial (LA) volume (top row) and LA volume index (bottom row) as demonstrated by boxplot (A, C) and direct comparison (B, D).
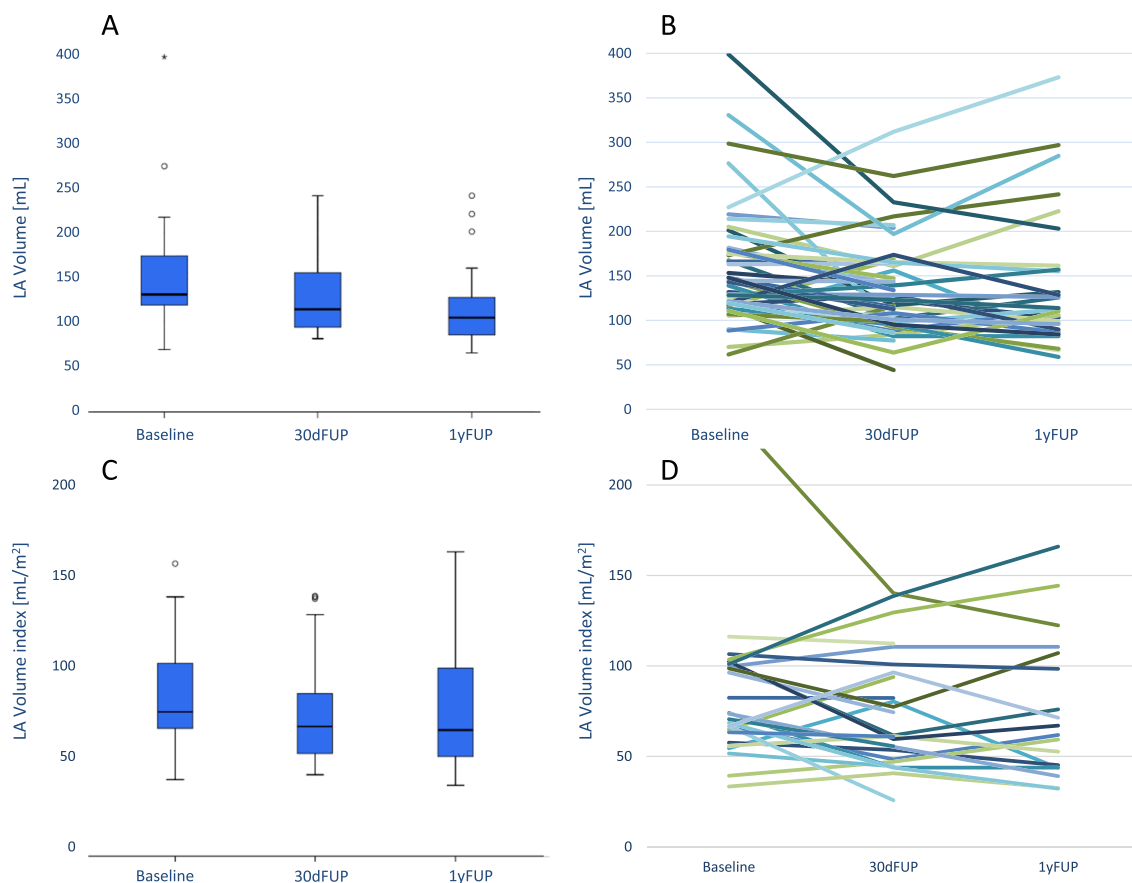

Table 3 Results

	n	Reduction	P
Baseline vs. 30dFUP			
ALPM (mm)	32	7.27 ± 5.40, CI 5.32 to 9.22	<0.001
AP (mm)	32	6.57 ± 5.33, CI 4.65 to 8.49	<0.001
LAV (mL)	32	36.61 ± 82.67, CI 6.81 to 66.41	0.018
LAVi (mL/m^2)	32	15.44 ± 40.98, CI 3.27 to 27.60	0.014
LVEDV (mL)	32	4.31 ± 52.33, CI −14.55 to 23.18	0.644
LVEDVi (mL/m^2)	32	−0.50 ± 48.10, CI −14.32 to 13.32	0.942
Baseline vs. 1yFUP			
ALPM (mm)	21	6.24 ± 5.70, CI 3.64 to 8.83	<0.001
AP (mm)	21	5.46 ± 4.99, CI 3.19 to 7.73	<0.001
LAV (mL)	21	37.03 ± 56.91, CI 11.13 to 62.94	0.007
LAVi (mL/m^2)	21	11.56 ± 31.87, CI 0.26 to 22.86	0.045
LVEDV (mL)	21	13.72 ± 58.42, CI −12.88 to 40	0.295
LVEDVi (mL/m^2)	21	17.75 ± 58.79, CI −2.15 to 37.64	0.079

ALPM, anterolateral to posteromedial extend; AP, anterior to posterior; CI, confidence interval; LAV, left atrial volume; LAVi, left atrial volume index; LVEDV, left ventricular end-diastolic volume; LVEDVi, left ventricular end-diastolic volume index.
Continuous variables are shown as mean ± standard deviation and categorical variables as number (%).

conclusive.[29] A prospectively designed randomized trial would be needed in order to elucidate the effect of the therapy on mitralvalve annulus dimensions and reverse atrial remodelling. Further answers might be given by the recently launched sham-controlled, double-blind Carillon Food and Drug Administration Trial (NCT03142152), aiming to recruit 350 (check) patients taking optimal medical therapy to the Carillon device or sham.

Figure 6 Evolution of left ventricular end-diastolic (LVED) volume (top row) and LVED volume index (bottom row) as demonstrated by boxplot (A, C) and direct comparison (B, D).
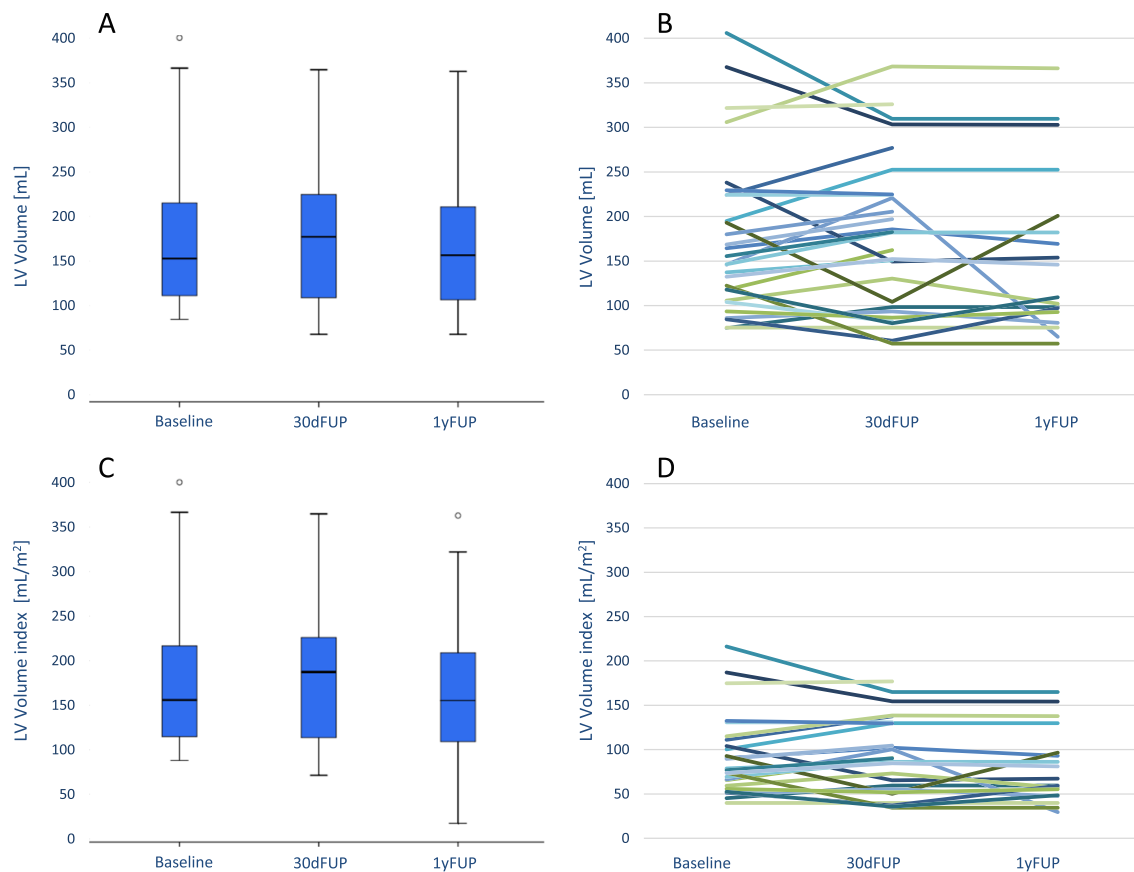
Conclusions

The CMCS reduces the diameter of the dilated mitral annulus as previously demonstrated in the AP dimension and also in APLM dimensions in our cohort. Furthermore, we saw an early and profound reduction in LAV and LAVi preceding similar effects on LVEDV and LVEDVi, suggesting that a reduction in mitral valve regurgitation leads via a reduction in LA pressure and geometry to a significant reverse left atrial remodelling that is visible as early as 30dFUP following a significant and stable reduction at 1 year follow-up.

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Conflict of interest

T.F.R. has received honoraria from Cardiac Dimensions, Inc. K.K.W. has been a recipient of the National Institute for Health Research (UK) Clinician Scientist Award; he is an investigator in randomized trials without financial compensation and has received speaker fees from Cardiac Dimensions, Inc. R.S.v.B. is a steering committee member and/or investigator for Cardiac Dimensions, Inc. in randomized trials without financial compensation and has received speaker fees from Cardiac Dimensions, Inc. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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