ORIGINAL RESEARCH

Circulatory Dynamics During Pulmonary Vein Isolation Using the Second-Generation Cryoballoon

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***Background*—**Circulatory dynamics change during pulmonary vein (PV) isolation using cryoballoons. This study sought to investigate the circulatory dynamics during cryoballoon-based PV isolation procedures and the contributing factors.

***Methods and Results*—**This study retrospectively included 35 atrial fibrillation patients who underwent PV isolation with 28-mm second-generation cryoballoons and single 3-minute freeze techniques. Blood pressures were continuously monitored via arterial lines. The left ventricular function was evaluated with intracardiac echocardiography throughout the procedure in 5 additional patients. Overall, 126 cryoapplications without interrupting freezing were analyzed. Systolic blood pressure (SBP) significantly increased during freezing (138.7±28.0 to 148.0±27.2 mm Hg, $P<0.001$) and sharply dropped (136.3±26.0 to 95.0±17.9 mm Hg, $P<0.001$) during a mean of 21.0±8.0 seconds after releasing the occlusion during thawing. In the multivariate analyses, the left PVs ($P=0.008$) and lower baseline SBP ($P<0.001$) correlated with a larger SBP rise, whereas a higher baseline SBP ($P<0.001$), left PVs ($P=0.017$), lower balloon nadir temperature ($P=0.027$), and female sex ($P=0.045$) correlated with larger SBP drops. These changes were similarly observed regardless of preprocedural atropine administration and the target PV order. PV occlusions without freezing exhibited no SBP change. PV antrum freezing without occlusions similarly increased the SBP, but the SBP drop was significantly smaller than that with occlusions ($P<0.001$). The SBP drop time-course paralleled the left ventricular ejection fraction increase (66.8±8.1% to 79.3±6.7%, $P<0.001$) and systemic vascular resistance index decrease (2667±1024 to 1937±513 dynes-sec/cm^2 per m^2, $P=0.002$).

***Conclusions*—**With second-generation cryoballoon-based PV isolation, SBP significantly increased during freezing owing to atrial tissue freezing and dropped sharply after releasing the occlusion, presumably because of the peripheral vascular resistance decrease mainly by circulating chilled blood. **(*J Am Heart Assoc*. 2017;6:e006559. DOI: 10.1161/JAHA.117.006559.)**

Key Words: atrial fibrillation • catheter ablation • cryoballoon • cryothermal physiology • pulmonary vein isolation

Pulmonary vein isolation (PVI) is a standard therapeutic intervention for atrial fibrillation.[1,2] Cryoballoon technology is becoming a major alternative owing to a less complicated technique, a shorter procedure time, and higher durability of the PVI compared with conventional radiofrequency catheter ablation.[3–5] The recently developed second-generation cryoballoon has exhibited a significantly higher performance than the first-generation cryoballoon owing to the improved cooling effect.[5,6] Multiple investigations have reported the noninferiority of the midterm outcome after the cryoballoon-based PVI (CBPVI) compared with radiofrequency.[5]

A successful CBPVI needs to occlude the entire proximal trunk of the targeted pulmonary vein (PV), which is completely different from point-by-point radiofrequency ablation. Because the myocardial injury is significantly more extensive after cryoballoon ablation than radiofrequency ablation,[7] the impact of an application on the circulatory dynamics should be much enhanced after the cryoballoon ablation. To date, however, no data have become available regarding the circulatory dynamics during CBPVI. The purpose of this study was to investigate the common pattern of circulatory dynamics during the CBPVI procedure and to elucidate the factors contributing to the circulatory change.

Methods

Study Population

We retrospectively enrolled atrial fibrillation patients who underwent their first PVI using second-generation

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Received May 19, 2017; accepted August 1, 2017.

Clinical Perspective

What Is New?

- This study clarified the circulatory dynamics during pulmonary vein isolation using second-generation cryoballoons, and they were characterized by a gradual rise in the systolic blood pressure (SBP) during the freezing phase and a sharp drop in the SBP after balloon deflation.
- The rise in the SBP was not observed during occlusions without freezing and was not affected by the administration of atropine sulfate or the order of the cryoballoon applications.
- The drop in the SBP was less sharp after freezing without an occlusion.
- The systemic vascular resistance significantly decreased along with the sharp drop in the SBP.

What Are the Clinical Implications?

- Our study results suggested (1) that the freezing of the atrial tissue might be the dominant reason for the SBP elevation and (2) that the leakage of the dammed chilled blood inside the pulmonary vein might be mainly associated with a sharp drop in SBP.
- This may contribute to understanding some aspects of the reaction to such stimulation and the nature of the circulatory dynamics during cryoballoon-based pulmonary vein isolation.

cryoballoons in our institute. From a total of 140 consecutive patients, we selected 35 in whom all 4 PVs were successfully isolated by a single 3-minute cryoapplication so as to eliminate the impact of the occlusion quality on the study results. We excluded 104 patients who required repeated cryoapplications to the same PV and 1 patient who exhibited a pain reaction during the cryoablation. Femoral arterial access was routinely acquired for continuous arterial pressure monitoring, and the heart rate and blood pressure (BP) were monitored throughout the procedure. The CBPVI was performed with a single 3-minute freeze technique, without a routine bonus application, using only large (28-mm) cryoballoons. In 5 additional patients, left ventricular (LV) function was evaluated with intracardiac echocardiography throughout the procedure. atrial fibrillation was classified according to the latest guidelines.[2] All patients gave their written informed consent. The study protocol was approved by the hospital's institutional review board. The study complied with the Declaration of Helsinki.

Ablation Procedure

All antiarrhythmic drugs were discontinued for at least 5 half-lives before the procedure. The surface ECG, bipolar intracardiac electrograms, and femoral intra-arterial BP were continuously monitored and stored on a computer-based digital recording system. The bipolar electrograms were filtered from 30 to 500 Hz. A 7F 20-pole 3-site mapping catheter was inserted through the right jugular vein for pacing, recording, and internal cardioversion.

The procedure was performed under moderate sedation obtained with dexmedetomidine. Immediately following venous access, 100 IU/kg body weight of heparin was administered, and heparinized saline was also infused to maintain the activated clotting times at 250 to 350 seconds. A single transseptal puncture was performed using an radiofrequency needle and an 8-Fr–long sheath. The transseptal sheath was exchanged over a guidewire for a 15-Fr steerable sheath. A 20-mm circular mapping catheter was used for mapping all PVs before and after the cryoablation to confirm electrical isolation. A spiral mapping catheter was used to advance the cryoballoon into the PV for support and mapping the PV potentials. When the left PVs (LPVs) were initially targeted (LPV-first group), atropine sulfate was always administered before ablation to anticipate bradycardia caused by a vagal reaction.[8] Following sealing at the PV antrum, complete occlusion was confirmed by injecting contrast medium. No 23-mm cryoballoons were used in any cases. This was followed by a freeze cycle of 180 seconds. No additional applications were performed after the isolation. To avoid bilateral phrenic nerve injury, all cryoballoon applications were applied under diaphragmatic electromyography monitoring.[9] When the balloon nadir temperatures exceeded −60°C or if phrenic nerve injury was suspected, the application was interrupted.[10] As the standard deflation technique, the intraballoon shaft was manually straightened when the intraballoon temperature reached 15°C to rewrap the balloon before deflation. The procedural end point was defined as an electrical PVI verified by the 20-mm circular mapping catheter.

Evaluation of the Circulatory Dynamics

The changes in the circulatory parameters were evaluated by comparing the systolic BP (SBP) and heart rate at specific time points: (1) every 1 minute during the 3-minute freezing phase ($T_{0\ min}$, $T_{1\ min}$, $T_{2\ min}$, and $T_{3\ min}$), (2) at 15°C for the in-balloon temperature during the thawing phase ($T_{15°C}$), (3) at the nadir of the BP after balloon deflation (T_{nadir}), and (4) during recovery of the BP at the baseline level ($T_{recovery}$). The elapsed time from $T_{15°C}$ to T_{nadir} and that from T_{nadir} to $T_{recovery}$ were also measured. An interval thaw time at 15°C was selected because that was generally the cryoballoon temperature limit at which the balloon was manually stretched by the operator on termination of the cryoballoon application. To examine the contributing factors, the

circulatory dynamics were evaluated under different conditions, as described below:

1. PV occlusion without freezing
   In 15 patients, the circulatory dynamics were evaluated during a 3-minute simple PV occlusion without freezing and after deflation (at least >2 minutes). The tests were all performed at the right superior PV (RSPV) before the start of the ablation procedure.
2. Order of the targeted PVs
   In 7 patients, the LPVs were initially targeted, followed by the right PVs (LPV-first group). In the remaining 28 patients, the right PVs (RPVs) were initially targeted, followed by the LPVs (RPV-first group).
3. Vagal denervation
   In 20 patients, including 7 patients in the LPV-first group, 0.5 mg atropine sulfate was given preprocedurally by intramuscular injection.
4. Freezing at the PV antrum without complete occlusion
   In 10 patients, 2-minute cryoapplications were applied at the left superior PV (LSPV) antrum without a complete LSPV occlusion, which was confirmed by a contrast injection, after the achievement of a PVI of all 4 PVs.

Evaluation of LV Function

In 5 additional patients, an intracardiac echocardiography probe was placed in the right ventricle for monitoring the LV wall motion in the longitudinal axis view throughout the procedure. The LV ejection fraction (LVEF) was measured by the Teichholz formula at specific time points: $T_{0\ min}$, $T_{3\ min}$, $T_{15°C}$, T_{nadir}, and $T_{recovery}$. The approximated systemic vascular resistance index (SVRI) was also calculated from the heart rate, echocardiographic calculated systolic volume (shown as SV), mean BP (shown as mBP), and body surface area (shown as BSA) using the following formula: $SVRI=80\times mBP/(SV\times heart\ rate\times 1000\times BSA)$.

Statistical Analyses

All statistical analyses were performed using R version 3.2.2 software (R Foundation for Statistical Computing). Continuous variables are reported as mean±SD and were compared using a Student *t* test. The estimated mean difference (EMD), with a 95% confidence interval (CI) followed by a *P* value, was described for every comparison of 2 groups. Differences between proportions were compared using Fisher exact tests. Differences in the mean values between ≥3 groups were evaluated by a Welch ANOVA. The changes in the circulatory parameters were compared by a paired *t* test for 1 group or a repeated ANOVA between classified groups. Because few data were available to predict the circulatory dynamics during freezing of a specific organ in a living body, we performed an exploratory calculation. A multiple regression analysis was performed (backward elimination method) to search for the factors affecting the SBP rise/drop from the possible candidates (clinical characteristics including age, sex, body mass index, left atrial volume, and in-procedural parameters including baseline SBP, in-balloon temperature, and target PV). All *P* values were 2-sided, and statistical significance was established at a $P<0.05$. All *P* values obtained from the Student *t* test, Welch ANOVA, and multiple regression analyses were verified by permutation tests.

Results

Procedural Results

The patient characteristics are shown in Table 1. In all patients, 4 PVs were successfully isolated by a single cryoballoon application. Of 140 cryoballoon applications, 15 were interrupted during 3-minute freezing. The remaining 125 applications (33 LSPVs, 33 left inferior PVs, 28 RSPVs, and 31 right inferior PVs) in which 3-minute freezing was applied without any interruption were further analyzed. Twenty-eight (22.4%) of 125 freezes were applied during atrial fibrillation. The mean nadir in-balloon temperature during the freezing phase was −51.4±7.0°C, and it significantly differed among the 4 PVs (−51.8±4.5°C in the LSPV, −47.4±4.0°C in the left inferior PV, −55.3±4.1°C in the RSPV, and −53.3±5.9°C in the right inferior PV, $P<0.001$). The mean interval between

Table 1. Clinical Characteristics of the Patients

Variable	Result (N=35)
Demographics	
Age, y	63.7±11.6
Male, n (%)	23 (66)
Height, cm	165.1±9.6
Body weight, kg	67.3±12.9
BMI, kg/m^2	24.3±3.0
BSA, m^2	1.74±0.20
Echocardiographic data	
LAD, mm	37.5±5.3
LAD index, mm/m^2	21.8±5.3
LAV, mL	44.7±12.5
LAV index, mL/m^2	25.8±7.0
LVDd, mm	45.4±4.3
LVDd index, mm/m^2	26.3±2.8
LVEF, %	67.3±6.1

BMI indicates body mass index; BSA, body surface area; LAD, left atrial diameter; LAV, left atrial volume; LVDd, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction.

Table 2. Changes in the Circulatory Dynamics in All 4 Pulmonary Veins

	LSPV (n=33)	LIPV (n=33)	RSPV (n=28)	RIPV (n=31)	*P* Value
SBP rise					
$T_{0\ min}$ to $T_{3\ min}$, mm Hg	11.1±18.3	13.5±12.8	7.8±11.7	4.2±11.7	0.031
SBP drop					
$T_{15°C}$ to T_{nadir}, mm Hg	−48.3±13.2	−39.0±12.6	−36.3±16.2	−40.7±16.9	0.011
$T_{3\ min}$ to $T_{15°C}$, s	42.4±14.1	33.2±8.9	48.4±8.7	36.6±10.6	<0.001
$T_{15°C}$ to T_{nadir}, s	23.3±8.1	19.6±5.3	18.3±11.8	22.5±5.0	0.042
T_{nadir} to $T_{recovery}$, s	32.9±13.4	28.7±8.4	31.3±12.8	31.6±12.9	0.614
	LSPV (n=25)	LIPV (n=26)	RSPV (n=23)	RIPV (n=23)	*P* Value
HR rise					
$T_{0\ min}$ to $T_{3\ min}$, beats/min	1.1±6.3	0.2±4.9	5.8±9.4	−2.8±9.7	0.003

HR indicates heart rate; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein; SBP, systolic blood pressure; $T_{0\ min}$, starting points of freezing; $T_{15°C}$, time points at 15°C for the in-balloon temperature during the thawing phase; $T_{3\ min}$, end points of freezing; T_{nadir}, time points at the nadir of the BP after balloon deflation; $T_{recovery}$, time points during recovery of blood pressure at the baseline level.

$T_{3\ min}$ to $T_{15°C}$ was 39.9 seconds, and the interval differed significantly among the 4 PVs (Table 2).

Circulatory Dynamics During the Freezing Phase

All SBP and heart rate data are plotted in Figure 1 individually for the 4 PVs. Of 125 PVs, the SBP increased from 138.7±28.0 to 148.0±27.2 mm Hg during the 3-minute freezing phase (EMD: 9.3 [95% CI, 6.7–11.8]; *P*<0.001). The time-course pattern of SBP was similar among the 4 PVs (*P*=0.11; Figure 2A); however, the magnitude of SBP rise differed significantly among the 4 PVs (*P*=0.031; Table 2) and was greater in LPVs than RPVs (12.0±15.7 versus 6.3±12.4 mm Hg; EMD: 5.7 [95% CI, 0.8–10.7]; *P*=0.026). SBP reached a plateau at $T_{1\ min}$ in the RPVs but continued to increase during the entire 3-minute freezing phase in the LPVs. A multiple regression analysis revealed that LPVs (*P*=0.008) and lower SBP at $T_{0\ min}$ (*P*<0.001) correlated with greater magnitude of SBP rise. The change in heart rate was analyzed in 97 applications (25 LSPVs, 26 left inferior PVs, 23 RSPVs, and 23 right inferior PVs) in which sinus rhythm was maintained throughout the application. The heart rate significantly increased from 61.9±12.2 to 67.7±11.7 beats/min during the freezing phase at the RSPV (EMD: −4.3 [95% CI, 0.5–8.1]; *P*=0.028) but did not significantly increase at the remaining 3 PVs (Figure 2B). This increase was observed during the first 1 minute of the freezing phase. The range of the distribution of SBP rise in the 4 PVs is described in Figure 3A.

Circulatory Dynamics During the Thawing Phase

During the thawing phase following the 3-minute freezing, the SBP gradually decreased until the manual stretch of the cryoballoon (at $T_{15°C}$) and rapidly dropped to the nadir thereafter (from 136.3±26.0 mm Hg at $T_{15°C}$ to 95.0±17.9 mm Hg at T_{nadir}; EMD: 41.3 [95% CI, 38.5–44.1]; *P*<0.001; Figure 2A). The mean interval from $T_{15°C}$ to T_{nadir} was 21.0±8.0 seconds. In the multiple regression analysis, higher SBP at $T_{0\ min}$ (*P*<0.001), LPVs (*P*=0.017), lower nadir balloon temperature (*P*=0.027), and female sex (*P*=0.045) significantly correlated with greater magnitude of SBP drop. In contrast, heart rate did not significantly change during the thawing phase (from 68.9±10.3 beats/min at $T_{15°C}$ to 68.9±13.5 beats/min at T_{nadir}; EMD: 0 [95% CI, −1.8 to 1.8]; *P*=1.000; Figure 2B). The magnitude of the SBP drop (*P*=0.011) and the interval between $T_{15°C}$ and T_{nadir} significantly differed (*P*=0.042), but the interval between T_{nadir} and $T_{recovery}$ was similar among the 4 PVs (*P*=0.614; Table 2). The range in the distribution of SBP drop in the 4 PVs is described in Figure 3B.

Impact of PV Occlusions Without Freezing

A 3-minute PV occlusion without freezing resulted in no BP change during the 3-minute occlusion phase (127.1±30.7 versus 126.3±29.4 mm Hg; EMD: 0.9 [95% CI, −2.6 to 4.4]; *P*=0.604) and after balloon deflation. Consequently, the magnitude of SBP change was significantly greater during occlusion (7.8±11.7 versus −0.9±6.3 mm Hg; EMD: 8.6 [95% CI, 2.3–14.9]; *P*=0.012) and after deflation using the standard cryoballoon application than during PV occlusion without freezing (Figure 4A).

Impact of the Order of Targeted PVs

The order of the targeted PVs did not significantly affect the magnitude of SBP rise during the freezing phase (RPV-first versus LPV-first: 9.2±14.4 versus 9.6±14.9; EMD: 0.4 [95% CI, −6.0 to 6.7]; *P*=0.909; Figure 5A) or of SBP drop during

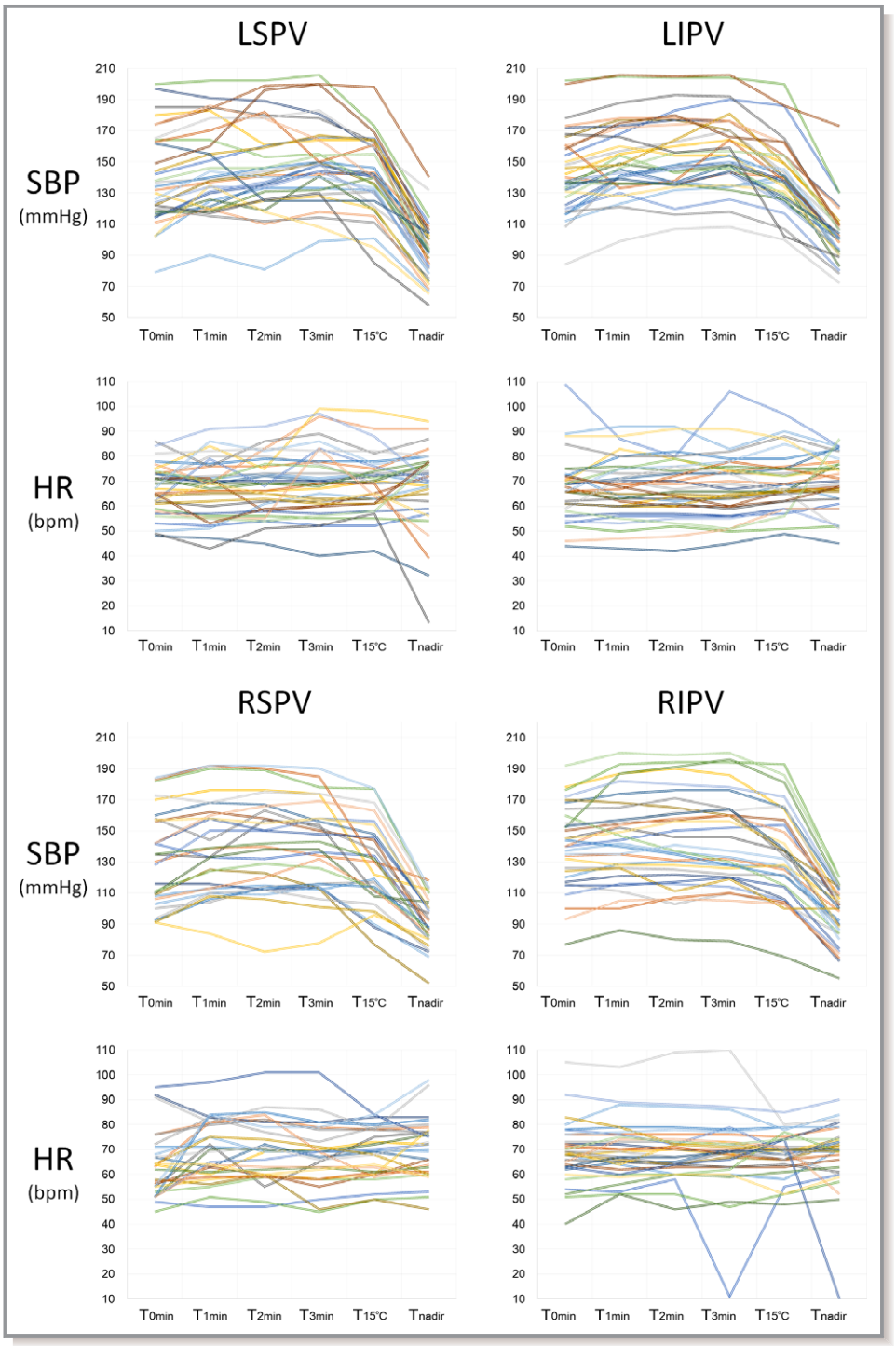

Figure 1. All data plots of the transition in SBP and HR during the freezing and thawing phases in the 4 pulmonary veins. HR indicates heart rate; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein; SBP, systolic blood pressure; T_{0min}, starting points of freezing; T_{1min}, 1 minute from T_{0min}; $T_{15°C}$, time points at 15°C for the in-balloon temperature during the thawing phase; T_{2min}, 2 minutes from T_{0min}; T_{3min}, end points of freezing; T_{nadir}, time points at the nadir of the BP after balloon deflation.

the thawing phase (RPV-first versus LPV-first: −40.5±15.7 versus −44.1±16.0 mm Hg; EMD: 3.6 [95% CI, −3.3 to 10.5]; *P*=0.305; Figure 5B). The results were similar for all 4 individual PVs.

Impact of a Preprocedural Atropine Administration

Administration of atropine did not affect the magnitude of SBP rise during the freezing phase (with versus without atropine:

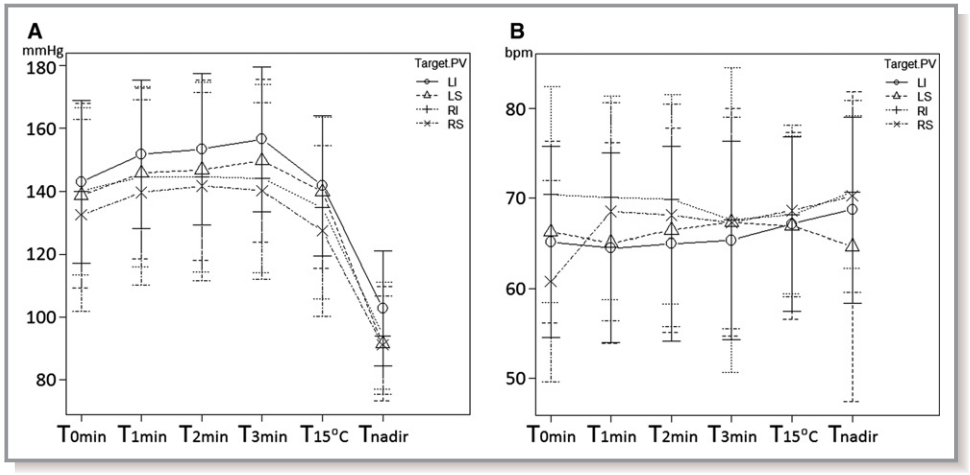

Figure 2. A transition of the systolic blood pressure (SBP) and heart rate (HR) during the freezing and thawing phases in the 4 pulmonary veins (PVs). A, The SBP rose during the freezing phase and recovered to the baseline level during the initial thawing phase, followed by a sharp drop after $T_{15°C}$ (time point at 15°C for the in-balloon temperature during the thawing phase). B, HR increased during the initial freezing phase at the right superior PV but did not at the remaining 3 PVs. LI indicates left inferior; LS, left superior; RI, right inferior; RS, right superior; T_{0min}, starting points of freezing; T_{1min}, 1 minute from T_{0min}; T_{2min}, 2 minutes from T_{0min}; T_{3min}, end points of freezing; T_{nadir}, time points at the nadir of the BP after balloon deflation; $T_{recovery}$, time points during recovery of blood pressure at the baseline level.

8.8±14.2 versus 9.8±14.8 mm Hg; EMD: 1.0 [95% CI, −4.2 to 6.1]; *P*=0.705; Figure 5C) or of SBP drop during the thawing phase (with versus without atropine: −43.2±15.6 versus −39.0±15.8 mm Hg; EMD: 4.2 [95% CI, −1.4 to 9.8]; *P*=0.139; Figure 5D). The results were similar among the 4 individual PVs.

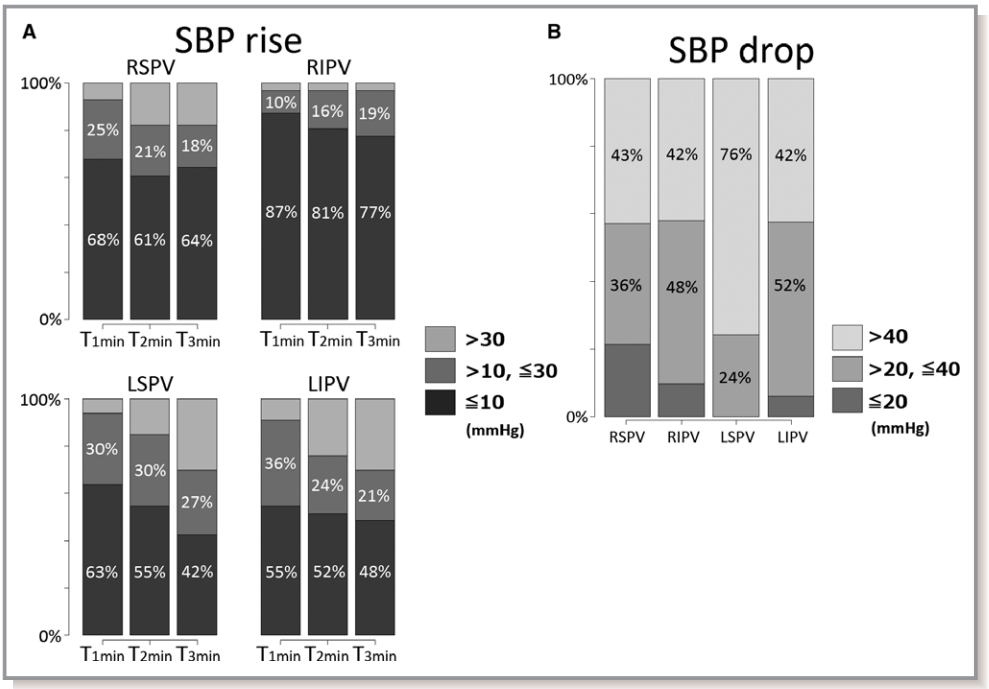

Figure 3. A, Percentage of applications with an SBP rise during the freezing phase. B, Percentage of applications with an SBP drop during the thawing phase. SBP indicates systolic blood pressure. LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein; T_{0min}, starting points of freezing; T_{1min}, 1 minute from T_{0min}; T_{2min}, 2 minutes from T_{0min}; T_{3min}, end points of freezing.

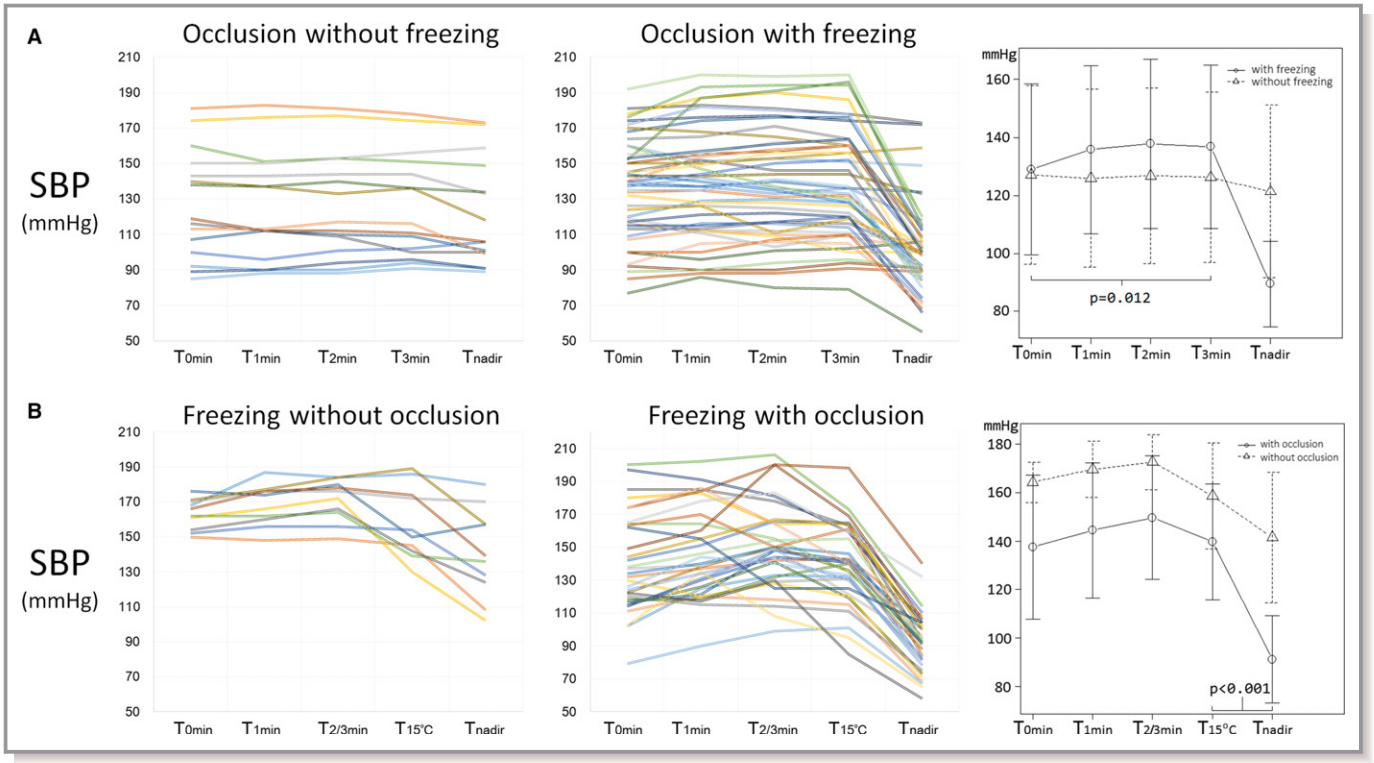

Figure 4. A, A simple pulmonary vein (PV) occlusion without freezing did not result in any systolic blood pressure (SBP) change during 3-minute occlusion or after deflation, which significantly differed from freezing with a PV occlusion. The right figure shows the mean value in each group. B, Nonoccluded freezing at the PV antrum resulted in a similar SBP rise during the freezing phase but a significantly smaller magnitude of the SBP drop during the thawing phase compared with freezing with a PV occlusion. The right figure shows the mean value in each group. T_{0min}, starting points of freezing; T_{1min}, 1 minute from T_{0min}; $T_{15°C}$, time points at 15°C for the in-balloon temperature during the thawing phase; T_{2min}, 2 minutes from T_{0min}; T_{3min}, end points of freezing; T_{nadir}, time points at the nadir of the BP after balloon deflation.

Impact of Freezing at the PV Antrum Without an Occlusion

The magnitude of SBP rise during the freezing phase (7.9±5.6 versus 11.1±18.3 mm Hg; EMD: 3.2 [95% CI, −8.7 to 15.1]; *P*=0.588) and of SBP decline from $T_{2\ min}$ (nonoccluded freezing) or $T_{3\ min}$ (occluded freezing) to $T_{15°C}$ (−14.2±15.7 versus −10.0±12.9; EMD: 4.2 [95% CI, −5.7 to 14.1]; *P*=0.392) was similar for nonoccluded and occluded freezes. However, the magnitude of the SBP drop from $T_{15°C}$ to T_{nadir} was significantly smaller in the nonoccluded freezes than in occluded freezes (−17.2±15.6 versus −48.3±13.2 mm Hg; EMD: 31.1 [95% CI, 21.1–41.2]; *P*<0.001; Figure 4B). The intervals between $T_{15°C}$ and T_{nadir} (11.8±9.3 versus 23.3±8.1 seconds; EMD: 11.6 [95% CI, 5.2–17.9]; *P*<0.001) and from T_{nadir} to $T_{recovery}$ (18.9±8.9 versus 32.8±13.4 seconds; EMD: 14.0 [95% CI, 3.8–24.2]; *P*<0.001) were significantly shorter in the nonoccluded than the occluded freezes.

LV Function

LV wall motion was evaluated during 20 freezes in 5 patients. Although there was no significant change in LVEF ($T_{0\ min}$ versus $T_{3\ min}$: 63.3±9.9 versus 62.3±9.3%; EMD: 0.9 [95% CI, −2.3 to 4.2]; *P*=0.557) and SVRI ($T_{0\ min}$ versus $T_{3\ min}$: 3487±1324 versus 3905±1510 dynes-sec/cm^2 per m^2; EMD: 418 [95% CI, −181 to 1017]; *P*=0.161) during the freezing phase, a significant increase in LVEF ($T_{15°C}$ versus T_{nadir}: 66.8±8.1% versus 79.3±6.7%; EMD: 12.4 [95% CI, 8.7–16.1]; *P*<0.001) and a decrease in SVRI ($T_{15°C}$ versus T_{nadir}: 2667±1024 versus 1937±513 dynes-sec/cm^2 per m^2; EMD: 730 [95% CI, 316–1144]; *P*=0.002) were observed during the thawing phase (Figure 6). These changes were observed following visualization of a hyperechoic bubble-like shadow in the LV just after balloon deflation, and then the time-course paralleled that of the change in the SBP.

Discussion

To the best of our knowledge, this report is the first to investigate circulatory dynamics during CBPVI. We found (1) that SBP tended to increase during the freezing phase and to recover to the baseline level during the initial thawing phase ($T_{3\ min}$ to $T_{15°C}$) and then dropped sharply following balloon deflation ($T_{15°C}$ to T_{nadir}), (2) that a PV occlusion alone did not result in any BP change, (3) that administration of atropine

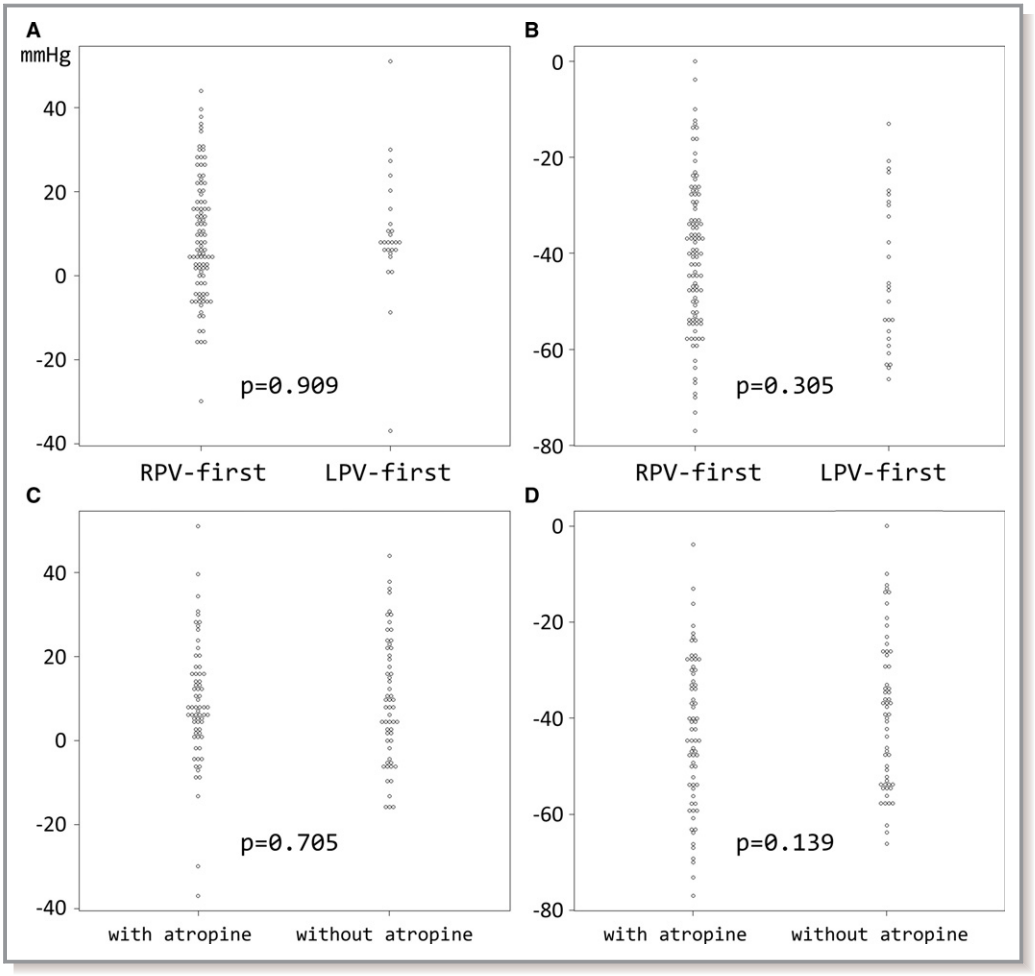

Figure 5. Effect of atropine and the order of the targeted pulmonary veins (PVs) on systolic blood pressure (SBP) change. The order of the targeted PVs did not significantly affect the SBP rise (A) or drop (B). Administration of atropine did not significantly affect SBP rise (C) and drop (D). LPV indicates left pulmonary vein; RPV, right pulmonary vein.

and the order of the targeted PVs did not affect this change, (4) that freezing at the PV antrum without a PV occlusion seemed to result in an SBP rise during the freezing phase but the magnitude of the BP drop ($T_{15°C}$ to T_{nadir}) during the thawing phase tended to be significantly smaller than that for freezing with a PV occlusion, and (5) that the time-courses of the increase in LVEF and the decrease in SVRI appeared to parallel those of SBP drop during the thawing phase. All *P* values calculated by the Student *t* test, Welch ANOVA, and multiple regression analyses were compatible with those from the permutation tests.

Circulatory Dynamics During Cryoballoon Ablation

The present study initially showed a rise in BP during the freezing phase, recovery of BP during the initial thawing phase, and a sharp drop in BP after releasing PV occlusion. Prior studies showed that cryoablation at the LSPV could result in bradycardia due to a vagal response during the thawing phase,[11] and this reaction disappeared with a preceding RSPV ablation.[8] In the present study, the order of the targeted PVs and vagal denervation by the administration of atropine did not have an impact on BP change, suggesting that the association of ganglionated plexi and the autonomic nervous system was limited. Simple PV occlusion without freezing did not result in any BP change, suggesting that mechanical stimulation (at the PV antrum) and damming of the blood flow in the PV might not have been responsible for this response. On the contrary, a nonoccluded tissue freeze tended to result in similar BP elevation during the freezing phase and smaller BP drop after balloon deflation than for occluded freezes. This result, together with the observation of a BP rise in all 4 PVs, suggests that freezing of atrial tissue might have resulted in BP elevation. Indeed, the elevated BP recovered to the baseline level during the initial thawing

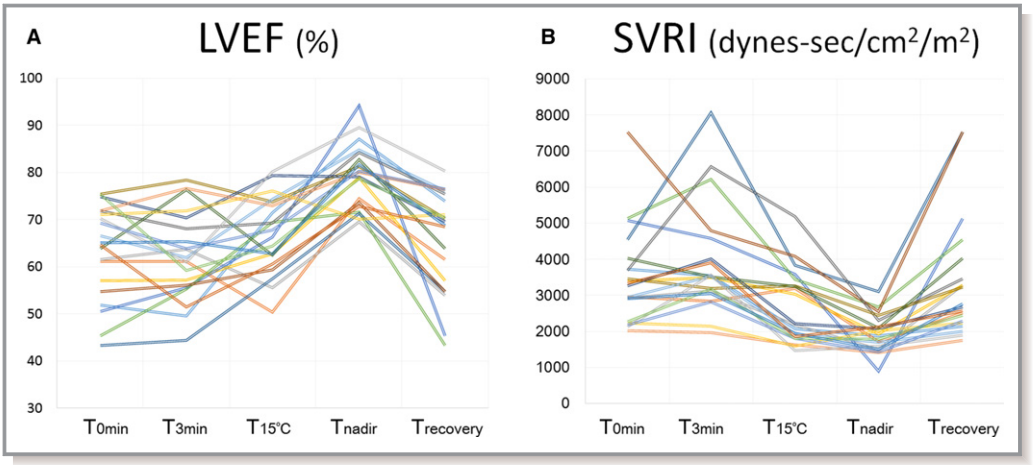

Figure 6. A, Transition of the LVEF during and after the cryoapplication. B, Transition of the SVRI during and after the cryoapplication. LVEF indicates left ventricular ejection fraction; SVRI, systemic vascular resistance index. T_{0min}, starting points of freezing; $T_{15°C}$, time points at 15°C for the in-balloon temperature during the thawing phase; T_{3min}, end points of freezing; T_{nadir}, time points at the nadir of the BP after balloon deflation; $T_{recovery}$, time points during recovery of blood pressure at the baseline level.

phase ($T_{3\ min}$ to $T_{15°C}$) before balloon deflation. The increase in heart rate during the initial freezing phase at the RSPV could be explained by the destruction of the efferent vagal neurons from the anterior right ganglionated plexus projecting onto the sinoatrial node by RSPV ablation.[8,12]

In contrast, a sharp BP drop was always initiated just after stretching of the balloon shaft between $T_{15°C}$ and balloon deflation, which was the timing of releasing the PV occlusion. That suggested that acute warming of the iced atrial tissue and leakage of the dammed chilled blood inside the PV appeared to be associated with the sharp BP drop. Because freezing without an occlusion tended to lack a deep nadir, the latter seemed to be the most likely mechanism for the sharp BP drop. Our study further clarified that the time-course of the sharp BP drop tended to parallel that of the decrease in SVRI and the increase in LVEF; the mean interval from $T_{15°C}$ to T_{nadir} was 21 seconds. Moreover, the balloon nadir temperature during freezing tended to correlate with the magnitude of the sharp BP drop, and the only predictor of the interval from $T_{15°C}$ to T_{nadir} was the magnitude of the BP drop. These data support the hypothesis that the chilled blood flow released from the occluded PV might have affected the peripheral circulation, and the magnitude of the BP drop depended on the amount of chilled blood flow. The slightly different magnitude of the BP change among the 4 PVs might be explained by the different balloon-tissue contact areas, different nadir balloon temperatures, and different amounts of dammed chilled blood inside the occluded PV, given anatomic variations. The not-so-negligible SBP decline in nonoccluded freezing could suggest that rapid thawing of the myocardial tissue also might have played some role in BP decrease after balloon deflation. Another possible explanation of circulatory alteration was the shunting of blood due to vasoconstriction, change in the preload of the left atrium due to the occlusion of one of the PVs, a change in the preload via the hepatic venous system by phrenic nerve pacing, and the impact on other organs via cold stimulus or humoral factors like cytokines.

Few data are available reporting the effect of the chilled blood flow and direct cryothermal stimulation of the circulatory system in humans. This might be caused by cooling peripheral receptors or specifically stimulating organs such as the brain. Ohta et al reported that brain hypothermia established by extracorporeal circulation decreased arterial pressure in sedated dogs.[13] Further investigation is necessary to clarify the fundamental physiology. This report may contribute to understanding some aspects of the reaction to such stimulation as well as the nature of the circulatory dynamics during the CBPVI.

Limitations

First, this study was a single-center retrospective study. Second, the number of participants was limited, especially in the echocardiographic study. The heart rate analysis was exclusively performed in 78% of the applications during which sinus rhythm was maintained; however, the results were consistent throughout the study population. Third, some potential contributing factors were not evaluated. Pain during the procedure might have affected circulatory change, although patients with pain were not included in the present study. We did not investigate any biomarkers such as catecholamines or cytokines. Fourth, the full cardiac hemodynamics were not evaluated and, the SVRI was calculated by an approximate formula.

Conclusions

In second-generation CBPVI, BP tended to increase significantly during the freezing phase and drop sharply after release of the occlusion during the thawing phase. Our study results suggested that direct cryothermal stimulation of the atrial tissue might result in a BP rise during freezing, whereas a decrease in peripheral vascular resistance by circulating chilled blood might be the main mechanism of the sharp BP drop during the thawing phase.

Acknowledgments

We would like to thank Mr John Martin for his help in the preparation of the manuscript.

Disclosures

None.

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