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ARTICLE *in* HEART RHYTHM: THE OFFICIAL JOURNAL OF THE HEART RHYTHM SOCIETY · FEBRUARY 2012

Impact Factor: 5.08 · DOI: 10.1016/j.hrthm.2012.01.025 · Source: PubMed

Epicardial ganglionated plexus stimulation decreases postoperative inflammatory response in humans

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BACKGROUND Surgical cardiac revascularization produces a high degree of systemic inflammation and the secretion of several cytokines. Intensive postoperative inflammation may increase the incidence of postoperative atrial fibrillation and favor organ dysfunctions. No data documenting the anti-inflammatory properties of epicardial vagal ganglionated plexus stimulation are available.

OBJECTIVE To verify the feasibility and safety of postoperative inferior vena cava-inferior atrial ganglionated plexus (IVC-IAGP) AQ: 3 burst stimulation and the effectiveness of this approach in reducing serum levels of inflammatory cytokines.

METHODS In 27 patients who were candidates for off-pump surgical revascularization, the IVC-IAGP was located during surgery, a temporary wire was inserted, and a negative atrioventricular node dromotropic effect was obtained in 20 patients on applying high-frequency burst stimulation. In 5 patients atrial fibrillation or phrenic nerve stimulation was induced, and the remaining 15 patients served as the experimental group. Twenty additional patients underwent off-pump surgical revascularization without IVC-IAGP stimulation and served as the control group. On arrival in the intensive care unit, the experimental group underwent IVC-IAGP stimulation for 6 hours. Blood samples were collected at different times.

RESULTS The serum levels of cytokines were not statistically different at baseline and on arrival in the intensive care unit between the groups, while they proved statistically different after 6 hours of stimulation: interleukin-6 (EG: 121 ± 71 pg/mL vs CG: 280 ± 194 pg/mL; $P = .001$), tumor necrosis factor-α (EG: 2.68 ± 1.81 pg/mL vs CG: 5.87 ± 3.48 pg/mL; $P = .001$), vascular endothelial growth factor (EG: 93 ± 43 pg/mL vs CG: 177 ± 86 pg/mL; $P = .002$), and epidermal growth factor (EG: 79 ± 48 pg/mL vs CG: 138 ± 76 pg/mL; $P = .019$).

CONCLUSIONS Prolonged burst IVC-IAGP stimulation after surgical revascularization appears to be feasible and safe and significantly reduces inflammatory cytokines in the postoperative period.

KEYWORDS Vagal stimulation; Cytokines; Inflammation; Cardiac surgery

ABBREVIATIONS AF = atrial fibrillation; **EGF** = epidermal growth factor; **GP** = ganglionated plexus; **ICU** = intensive care unit; **IL** = interleukin; **IVC-IAGP** = inferior vena cava-inferior atrial ganglionated plexus; **MCP-1** = monocyte chemotactic protein-1; **TNF-α** = tumor necrosis factor-α; **VEGF** = vascular endothelial growth factor

Introduction

Surgical trauma and ischemia-reperfusion during cardiac revascularization trigger systemic inflammation and the release of cytokines into the serum.[1] While inflammatory activation may favor the healing of surgical injuries, it may, at the same time, induce organ dysfunctions and postoperative complications.[2]

Corticosteroid administration has been proved to reduce postoperative systemic inflammation, the incidence of postoperative atrial fibrillation (AF), and the need for mechanical ventilation[3]; however, side effects of this treatment have been described.[3,4] Although improved operative approaches have been shown to reduce inflammatory stimuli,[5] the modulation of an excessive inflammatory response constitutes a clinical challenge.

Neural mediators strongly modulate inflammatory processes through the so-called cholinergic anti-inflammatory pathway.[6] This endogenous system may be potentiated by vagal trunk stimulation, thereby yielding advantages in the treatment of inflammatory diseases.[7] Although vagal trunk

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1547-5271/$ -see front matter © 2012 Heart Rhythm Society. All rights reserved. doi:10.1016/j.hrthm.2012.01.025

stimulation is a fascinating approach to vagal tone augmentation, it is difficult to implement in the operating theater, as it requires the use of dedicated electrodes and an additional surgical trauma to isolate the cervical vagal trunk. Stimulation of epicardial ganglionated plexuses (GPs) could be an alternative to vagal trunk stimulation. However, no data supporting the anti-inflammatory properties of this approach are as yet available.

We previously described high-frequency inferior vena cava-inferior atrial ganglionated plexus (IVC-IAGP) stimulation by means of a temporary bipolar wire implanted into the epicardial fat pad in the early postoperative period.[8] Moreover, we confirmed the efficacy of high-frequency stimulation delivered in bursts within the atrial refractory period in augmenting vagal tone, without inducing AF, in humans.[9,10]

The aims of the present study were twofold: first, to verify the feasibility of prolonged IVC-IAGP burst stimulation in the postoperative period; second, to demonstrate the efficacy of this approach in modulating the release of inflammatory cytokines into the serum.

Methods

Study population

Patients undergoing off-pump coronary artery bypass graft were enrolled at the time of surgery. The inclusion criteria were as follows: (1) multivessel coronary disease, (2) ejection fraction >45%, (3) absence of significant valvular dysfunction, (4) normal kidney and liver function, (5) sinus rhythm during intervention and PR interval <200 ms, (6) no history of AF, and (7) absence of other significant comorbidities.

All patients signed an informed consent form, which had been approved by the local ethics committee.

Twenty-seven consecutive patients were enrolled in order to obtain a group of 20 subjects for the analysis of postoperative stimulation. Furthermore, a matched-control group of 20 patients was enrolled in order to collect postoperative data.

Anesthesia and surgical technique

Anesthesia was induced and maintained by the intravenous infusion of sufentanil citrate and propofol. Muscle relaxation was achieved with vecuronium bromide. Heparin (300 U/kg) was administered as an anticoagulant and was neutralized by protamine after the completion of anastomoses. All patients underwent a median sternotomy. The internal thoracic artery was harvested by means of a skeletonized technique, and saphenous veins were harvested as grafts. The Octopus tissue stabilization system (Medtronic Inc, Minneapolis, MN) was used to stabilize the target coronary vessels. An intracoronary shunt was used for all coronary anastomoses.

Wire placement and intraoperative protocol

In all patients in the experimental group, on completion of anastomoses 2 temporary epicardial unipolar ventricular wires (Streamline Convenience model 6494, Medtronic) were placed on the right ventricle for backup ventricular pacing. The right inferior vagal fat pad was exposed by means of gentle traction of the right atrium in order to obtain an optimal view of the fat-covered zone (fat pad). This area is located across Sondergaard's groove, close to the junction of the right inferior pulmonary vein and the left atrium, and extends about 2 cm toward the inferior vena cava. A bipolar temporary wire (Streamline Convenience model 6495 Medtronic, or Myopace model 50060T, FIAB, Florence, Italy) was directly inserted into the fat pad with the distal pole emerging near the connection of the right inferior pulmonary vein with the left atrium (Figure 1). The bipolar wire was connected to an external custom-made high-frequency stimulator developed by using the LabView system (National Instruments, Houston, TX). The atrium was constantly paced at 90 pulses/min (with 1 ms pulse duration). The system was capable of delivering a train of pulses (pulse rate 50 Hz; pulse duration 1 ms; train duration 180 ms) synchronized with the pacing stimulus. This pattern of synchronized-burst high-frequency stimulation enables autonomic nerve fibers to be excited during the absolute atrial refractory period while minimizing the risk of inducing AF.[9,10] Pulse amplitude was increased in 1-V steps (from 1 to 9 V) after every 5 bursts. Voltages resulting in PR interval lengthening (at least 30% in relation to the basal value) and advanced atrioventricular block (2:1 or complete block) were assessed (Figure 2). If an arrhythmia was induced, stimulation was immediately interrupted and direct atrial defibrillation was performed by means of internal paddles. In the event of an unsatisfactory negative dromotropic effect, further sites (up to 5) were tested in the same area of the fat pad.

An electrocardiogram recorder (speed 50 mm/s) was used to measure the PR interval. The mean PR interval (calculated before burst stimulation over 5 atrial-paced cardiac cycles) was compared with the mean value of the 5 cycles recorded during burst stimulation for each voltage step.

In control group patients, temporary wires for atrial pacing were sutured to the right free wall, as is routinely performed.

Postoperative stimulation

On arrival in the intensive care unit (ICU), electrocardiogram and invasive arterial blood pressure monitoring was initiated. Patients were ventilated, and propofol was continuously infused for at least 6 hours.

In all patients in the experimental group who had shown a negative dromotropic effect during intraoperative tests and no arrhythmias or extracardiac stimulation on high-frequency stimulation, the following stimulation protocol was applied. Backup ventricular pacing was ensured at 40 beats/min. High-frequency stimulation was initiated (90 bursts/min; pulse rate 50 Hz; pulse duration 1 ms; train duration 180 ms) through the wires inserted into the fat pad and continuously delivered for 6 hours after arrival in the ICU. The voltage was set at a value that resulted in PR interval lengthening of at least 30%. Every

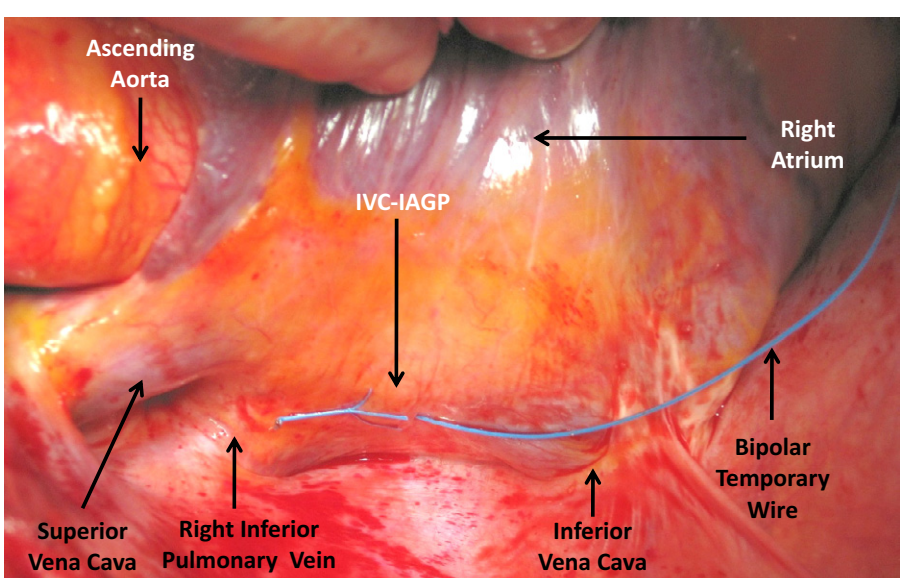

Figure 1 Off-pump surgical picture showing posterior view of the right atrium, fat pad area, and temporary wire implanted into the inferior vena cava-inferior atrial ganglionated plexus (IVC-IAGP). The anatomical relation among ascending aorta, superior and inferior vena cava, and right inferior pulmonary vein is also visible.

hour, the correct delivery of stimulation was verified and the voltage was adjusted to maintain the PR interval lengthening. Patients in the control group were constantly paced at 90 pulses/min in the atrium.

Blood sampling and measurements

Blood samples (10 cm^3) from all patients were collected in tubes containing granule separators and clot activators (FL Medical, Italy) at the baseline before skin incision (T1), on arrival in the ICU (T2), and after 3, 6, 9, and 12 hours (T3, T4, T5, and T6, respectively). Samples were centrifuged (4000*g* for 10 min), and serum was stored in aliquots at −20°C until assay. Levels of interleukins (IL-6, IL-10), tumor necrosis factor-α (TNF-α), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and monocyte chemotactic protein-1 (MCP-1) were determined by means of commercially available enzyme-linked immunosorbent (Cytochine Biochip Array Technology, Evidence Investigator, Randox Laboratories, Crumlin, UK) in accordance with the manufacturer's instructions.

Moreover, following blood pressure values were measured at the times of blood sampling in the ICU: arterial pressure (systolic and diastolic), pulmonary artery pres-

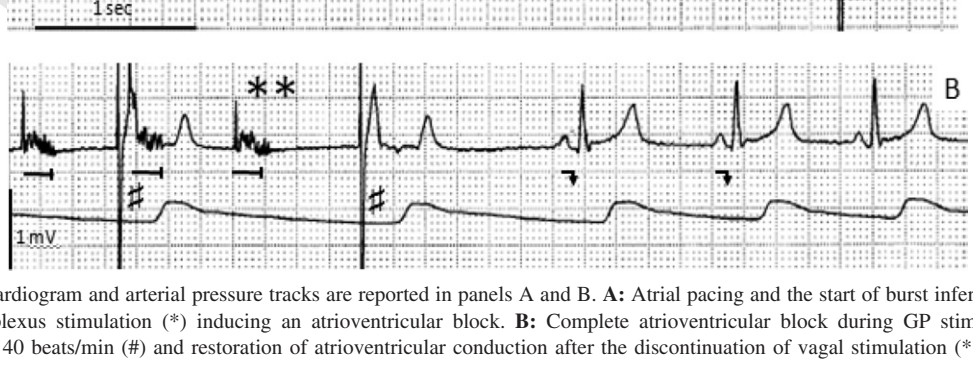

Figure 2 Electrocardiogram and arterial pressure tracks are reported in panels A and B. **A:** Atrial pacing and the start of burst inferior vena cava-inferior atrial ganglionated plexus stimulation (*) inducing an atrioventricular block. **B:** Complete atrioventricular block during GP stimulation, with backup ventricular pacing at 40 beats/min (#) and restoration of atrioventricular conduction after the discontinuation of vagal stimulation (**).

Table 1 Parameters of the 2 groups of patients (n = 35)

Baseline parameters	Control group (n = 20)	Experimental group (n = 15)	*P*
Sex: Man	16 (80)	10 (66)	.451
Age (y)	64 ± 10	67 ± 7	.328
Body surface area (m^2)	1.9 ± 0.2	1.8 ± 0.2	.153
Hypertension	15 (75)	11 (73)	.489
Previous myocardial infarction	1 (5)	1 (7)	1.000
Baseline PR interval (ms)	158 ± 25	153 ± 24	.556
Left ventricular ejection fraction (%)	54 ± 9	56 ± 6	.462
Left ventricular end systolic diameter (mm)	33 ± 3	33 ± 5	.792
Left ventricular end diastolic diameter (mm)	49 ± 3	47 ± 3	.159
Left atrium diameter (mm)	40 ± 4	39 ± 4	.469
Use of beta-blockers	18 (90)	12 (80)	.631
Use of ACE inhibitors or angiotensin-receptor blockers	16 (80)	12 (80)	.631
Use of statins	20 (100)	13 (87)	.176
Intraoperative data			
Number of grafts	3 ± 1	3 ± 1	1.000
Operating time (min)	230 ± 37	229 ± 33	.935
Postoperative data			
Maximum serum level of troponin I (pg/mL)	0.76 ± 1.22	1.08 ± 1.33	.465
Maximum leukocyte number (mm^3)	18,005 ± 5,780	19,923 ± 7,016	.382
Length of intensive care unit stay (h)	31 ± 16	29 ± 19	.738
Postoperative atrial fibrillation	5 (25)	1 (7)	.207

Data are expressed as either mean ± SD or as number and percentage.
ACE = angiotensin-converting enzyme.

sure (systolic and diastolic), and mean central venous pressure.

Postoperative clinical follow-up

Troponin I serum levels and blood cell counts were measured on arrival in the ICU, at 12 and 24 hours after surgery, and daily for 5 days; AF occurrence and length of ICU stay were also recorded. Cardiac wires were removed manually by means of gentle traction on the fifth postsurgery day.

Statistical analyses

Continuous data are expressed as mean ± standard deviation, and categorical variables as percentages. The skewness of continuous data was checked by means of a Shapiro-Wilk test, and distributions were compared by Wilcoxon nonparametric test or Student *t* test, as appropriate. Differences in proportions were compared by using χ^2 analysis. Serum cytokine levels and blood pressure values were compared by using 2-way analysis of variance for repeated measures. A *P* value of $<.05$ was considered significant. Statistical analyses were performed by using SPSS software (version 12.0, SPSS, Inc, Chicago, IL).

Results

Intraoperative and postoperative protocols

The right inferior vagal fat pad was located and exposed in all patients of the experimental group (27 patients). In 20 patients (74%), a satisfactory negative atrioventricular node dromotropic effect was obtained on applying high-frequency burst stimulation through the wires inserted into the fat pad. The mean number of attempts required to successfully place the pacing wires was 2 ± 1, the first attempt being successful in 13 of the 20 cases (65%). In the remaining 7 cases, vagal reflex was not evoked after 5 positioning attempts. In 3 patients, AF was induced when high-frequency stimulation was delivered at 7 V, and in 2 patients, right phrenic nerve stimulation was observed. The burst amplitudes required to obtain PR interval lengthening and advanced atrioventricular block were 3.8 ± 1.8 and 5.4 ± 2.0 V, respectively. No ventricular arrhythmias were induced.

In the postoperative phase, high-frequency stimulation was applied in the 15 patients with vagal reflex and no AF or phrenic nerve stimulation. During 6 hours of stimulation, no adverse events were reported and no episodes of AF were observed. The voltage required to evoke vagal reflex did not change in the postoperative phase, and the PR interval lengthening was constantly maintained for 6 hours. The sinus heart rate was <90 pulses/min in all patients; thus, the burst stimulation resulted in fixed overdrive pacing. Similarly, standard atrial pacing resulted in fixed-rate overdrive (at 90 pulses/min) in the control group.

Comparisons between groups

No differences in demographic and clinical characteristics were noted between the groups (Table 1). The number of T1 grafts was comparable between the experimental and control groups (3 ± 1 vs 3 ± 1; $P = 1.000$) as was the operating time (230 ± 37 min vs 229 ± 33 min; $P = .935$) (Table 1).

Compared with baseline (T1), the levels of IL-6 and IL-10 were significantly higher in both groups during ICU stay (from T2 to T6; all $P < .05$). Similarly, significantly higher values of MCP-1 were observed at T5 and T6 in the 2 groups (all $P < .05$). At T4, T5, and T6, the experimental

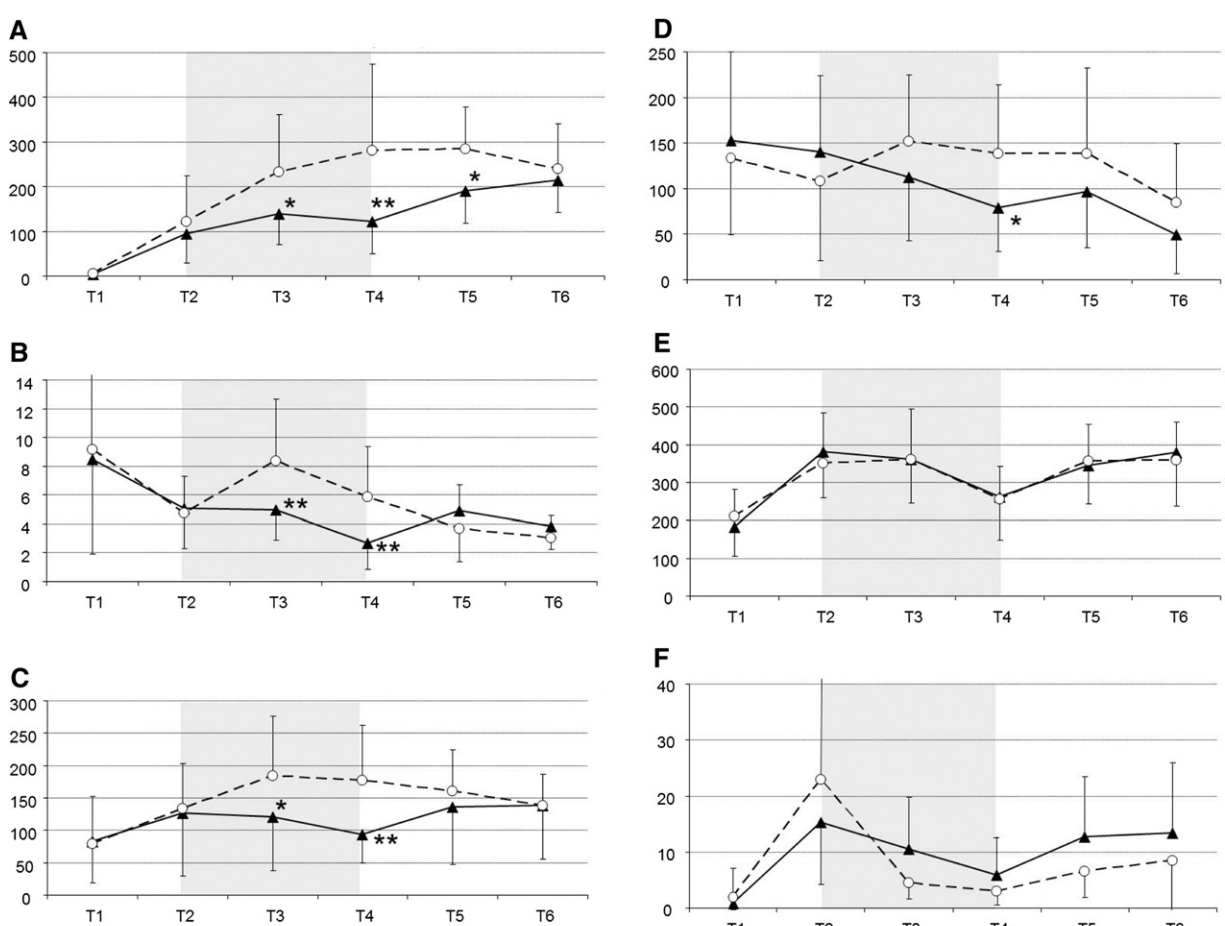

Figure 3 Comparison of serum cytokine levels in the experimental and control groups. **A:** interleukin-6; **B:** tumor necrosis factor-α; **C:** vascular endothelial growth factor; **D:** epidermal growth factor; **E:** monocyte chemotactic protein-1; **F:** interleukin-10. Values are in picograms per milliliter. T1: baseline assessment before skin incision; T2: arrival in the intensive care unit (ICU); T3, T4, T5, and T6: 3, 6, 9, and 12 hours after arrival in the ICU, respectively. Gray zones between T2 and T4 indicate burst inferior vena cava-inferior atrial ganglionated plexus stimulation time. *P* values vs control group: $^{*}P < .05$; $^{**}P < .01$ (2-way analysis of variance for repeated measures).

group displayed significantly lower concentrations of TNF-α (all $P < .05$) compared with baseline, as well as lower levels of EGF (all $P < .01$), whereas no differences were noted in the control group.

Serum cytokine levels were not significantly different between the groups, either at the baseline or on arrival in the ICU (Figure 3).

After 3 hours of stimulation, the experimental group displayed significantly lower values of IL-6 (138 ± 68 pg/mL vs 234 ± 128 pg/mL; $P = .014$), TNF-α (4.98 ± 2.11 pg/mL vs 8.37 ± 4.31 pg/mL; $P = .009$), and VEGF (121 ± 83 pg/mL vs 184 ± 93 pg/mL; $P = .046$) than did the control group. These differences were much more evident at 6 hours: IL-6 (121 ± 71 pg/mL vs 280 ± 194 pg/mL; $P = 0.004$), TNF-α (2.68 ± 1.81 pg/mL vs 5.87 ± 3.48 pg/mL; $P = .003$), and VEGF (93 ± 43 pg/mL vs 177 ± 86 pg/mL; $P = .002$). Furthermore, significantly lower values of EGF were also observed at 6 hours in the experimental group (79 ± 48 pg/mL vs 138 ± 76 pg/mL; $P = .012$).

The serum concentrations of IL-6, TNF-α, VEGF, and EGF at 3 and 6 hours after stopping IVC-IAGP stimulation (T5 and T6, respectively) progressively returned to the values of the control group (see Figure 3). Indeed, IL-6 serum levels at T5 and T6 were 189 ± 72 and 215 ± 73 pg/mL vs 284 ± 94 pg/mL ($P = .038$) and 239 ± 102 pg/mL ($P = .576$); TNF-α values were 4.9 ± 1.9 and 3.8 ± 1.6 pg/mL vs 3.7 ± 2.3 pg/mL ($P = .250$) and 3.1 ± 1.5 pg/mL ($P = .318$); VEGF values were 135 ± 88 and 138 ± 83 pg/mL vs 160 ± 64 pg/mL ($P = .519$) and 139 ± 49 pg/mL ($P = .988$); EGF values were 96 ± 61 and 50 ± 43 pg/mL vs 138 ± 94 pg/mL ($P = .287$) and 85 ± 65 pg/mL ($P = .200$).

No differences in MCP-1 and IL-10 levels were noted between the groups during and after stimulation.

During ICU stay, no differences in blood pressure values were observed between the groups (Figure 4).

Postoperative clinical follow-up

Before discharge, AF occurred in 5 patients (25%) in the control group and 1 patient (7%; $P = .207$) in the experi-

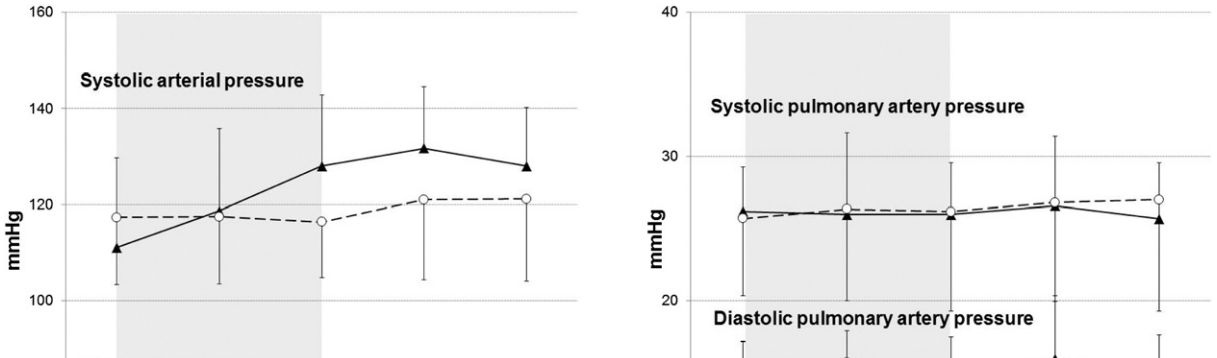

Figure 4 Comparison of blood pressure values in the experimental and control groups. T2: arrival in the intensive care unit (ICU); T3, T4, T5, and T6: 3, 6, 9, and 12 hours after arrival in the ICU, respectively.

mental group (13 hours after the interruption of stimulation). Patients who developed AF during intraoperative tests did not suffer AF in the postoperative period. Among the 7 patients in whom a vagal reflex was not inducible, only 1 had AF during follow-up.

No differences in the length of ICU stay or in the maximum serum troponin I and leukocyte levels were noted (Table 1). No adverse events occurred during cardiac wire removal before discharge.

Discussion

Main findings

This study provides the first evidence of postoperative inflammatory response modulation by means of epicardial GP stimulation and is the first experience of prolonged intrinsic cardiac nerve stimulation in humans. Six hours of burst IVC-IAGP stimulation significantly decreased IL-6, TNF-α, VEGF, and EGF. Moreover, prolonged burst IVC-IAGP stimulation after surgical revascularization appeared feasible and safe.

Temporary wire implantation and stimulation protocol

Temporary wire implantation was easy and rapid. The operating time was comparable between the experimental and control groups. Indeed, as we previously measured,[8] the mean time needed to locate the IVC-IAGP and to implant the pacing wire does not exceed 5 minutes. In this study, the IVC-IAGP was identified in 65% of the cases at the first site tested, without inducing intraoperative or postoperative side effects in the majority of subjects (56%). In some cases, right phrenic nerve stimulation (7%) was observed, and in the framework of this study, stimulation was interrupted and the patient was excluded from the analysis. However, for clinical application, various techniques may be proposed to overcome this kind of issue, such as electrically isolating the nerve. AF was also induced during intraoperative GP stimulation (11%), as previously reported in animal experiments.[11] In the present study, AF was induced by applying $\geq$7 V; thus, a voltage higher than that is needed to modulate atrioventricular nodal conduction (3.8 $\pm$ 1.8 V). This observation in humans confirms experimental data showing that acute AF induction by vagal stimulation is voltage dependent[12] and suggests that the IVC-IAGP could also be effectively stimulated in subjects who experience AF during acute tests.

However, no patients developed postoperative AF during GP stimulation, and a trend toward lower AF incidence (25% vs 7%) was observed in the postoperative period, possibly as a consequence of lower systemic inflammation. Indeed, inflammation of the atrium after cardiac surgery is associated with inhomogeneity of atrial conduction and AF.[13]

Finally, the variability of the anatomical arrangement and distribution of the epicardial intrinsic vagal network could explain the lack of vagal reflex on stimulation in 26% of the cases.[14] Extending mapping to include other GPs could possibly reduce this percentage.

In this preliminary experience, the postoperative IVC-IAGP stimulation seemed safe in terms of possible hemodynamic effects. Indeed, blood pressure values measured in the ICU were not affected by stimulation. Nonetheless, larger studies are warranted in order to confirm our results.

Ganglionated plexus stimulation and cytokine secretion

The vagus nerve is known to modulate systemic and local inflammatory processes.[6] Acetylcholine released from efferent vagal fibers suppresses the production and secretion of inflammatory cytokines[6,15] by acting through the α7 subunit of the nicotine acetylcholine receptor (α7nAChR) expressed on immunocytes and organ tissues such as coronary microvascular endothelial cells, cardiomyocytes, and smooth vascular cells. The binding of acetylcholine to the α7nAChR activates Janus kinase 2 and activators of transcription 3 that compete with a key nuclear transcription factor for the syntheses of proinflammatory cytokines.[6,15] Vagal trunk stimulation is an emerging strategy to treat inflammatory diseases and has yielded favorable effects in animal models of sepsis,[16] hemorrhagic shock,[17] postoperative ileus,[18] and burn-induced organ dysfunction[19] in the acute phase of myocardial ischemia/reperfusion injury[20] and in heart failure.[21,22]

Surgical trauma due to cardiac revascularization typically increases serum cytokine levels; these reach a peak during the early postoperative period,[23] though the intensity of the inflammatory response depends on the cytokine promoter gene polymorphisms.[24] In particular, in our study we performed postoperative IVC-IAGP stimulation for 6 hours after surgery when clinically relevant inflammatory cytokines (IL-6, TNF-α) reach their peak,[23] as also confirmed by our results.

Intense inflammatory response may cause postoperative clinical complications, resulting in slower recovery, prolonged ICU stay, and higher incidence of postoperative AF,[23] and may lead to inflammatory tissue infiltration.[13] We did not record any differences in ICU stay time; however, a trend toward a lower incidence of postoperative AF (25% vs 7%) was observed, though the number of patients enrolled was not large enough to reach statistical significance. A specific study, designed to better verify this observation, could be interesting. Typically, the serum level of IL-6 progressively increases from the basal value to the sixth hour after arrival in the ICU (peak time), as documented by previous papers[23] and confirmed by our control group data. In our study, no differences were seen in IL-6 at T1 and T2 between the experimental and control groups, while a significant reduction was found at the third (T3) and sixth (T4) hours of IVC-IAGP stimulation (see Figure 3). The strong biological influence of GP stimulation on IL-6 secretion is further supported by the analysis of the serum levels at T5 and T6, which progressively reached the typical control group curve. These data could be interpreted as a consequence of the loss of the secretory inhibition caused by acetylcholine released from vagal fibers during high-frequency stimulation. IL-6, an inflammatory mediator with pleiotropic effects, is involved in reducing myocardial contractility, activating leukocytes, inducing intracellular adhesion molecules,[25] and inducing arrhythmias during the ischemia-reperfusion process.

The activation of α7nAChR by acetylcholine leads to the inhibition of nuclear factor-κB (p65) translocation from the cytoplasm to the nucleus,[26] resulting in the reduced expression not only of IL-6 but also of TNF-α. Our data are coherent with these findings, as differences in TNF-α between the groups were also significant at the third and sixth hours (see Figure 3). TNF-α is an important inflammatory cytokine; not only is it associated with decreased myocardial contractility and coronary flow, as a result of a nitric oxide–dependent mechanism,[27] but it is also implicated in the pathogenesis of programmed myocardial cell death.[28]

Modulation of IL-6[29] and TNF-α[30] secretion may indirectly control VEGF and EGF expression. Indeed, IVC-IAGP stimulation produced a progressive reduction in VEGF and EGF serum levels, which displayed a clear difference after 6 hours of stimulation. The growth factors VEGF and EGF are powerful angiogenic molecules that help to repair vascular injures; at the same time, however, they are able to increase endothelial permeability and to exhibit several proinflammatory and procoagulant activities.[31]

The serum levels of TNF-α, VEGF, and EGF also progressively followed the curve seen in the control group (see Figures 3B-3D), further suggesting a real effect of IVC-IAGP stimulation and the potential role of this postoperative treatment.

Animal and in vitro studies have shown that acetylcholine or vagal stimulation does not reduce IL-10 expression[6]; our results confirm this finding (see Figure 3). IL-10 exerts cardioprotective functions by inhibiting neutrophil-endothelial interaction, myocardial ischemia/reperfusion injury,[32] and vascular muscle proliferation[33]; it also favorably inhibits the adverse effects of TNF-α.[34]

Although we did not perform a detailed characterization of the impact on hemodynamic parameters, the effect of IVC-IAGP stimulation on inflammatory cytokines does not seem secondary to physiologic changes. Indeed, both groups were constantly paced in the atrium at the same rate, and no differences were observed in blood pressure values during and after stimulation.

Clinical implications

The present approach may favor the transfer of the advantageous biological effects yielded by vagal network stimulation after cardiac surgery to humans; it may also promote a better understanding of the role of the neuroautonomic system in postoperative complications, such as multiorgan dysfunctions due to intense systemic inflammation. More prolonged GP stimulation (48−72 hours) could reduce the incidence of postoperative AF by attenuating inflammation and lowering sympathetic activity.

Finally, this proof-of-concept study could encourage future investigations into the possible advantages of intrinsic GP stimulation in subjects affected by heart failure, as an alternative approach to cervical vagal trunk stimulation.

Study limitations

The present results show that this approach can be applied only in a subgroup of patients (74%). Further research could investigate whether it is possible to overcome this limitation by switching to left-side GPs or by implementing transvenous vagal trunk stimulation.

Moreover, we did not examine possible changes in left ventricular function markers between the 2 groups. However, recent findings seem to exclude any effect of intrinsic GP stimulation on hemodynamic parameters such as left ventricular contractility, lusitropy, and left ventricular and aortic pressure.[35]

The present analysis was performed in a small population and patients were not randomized; this should be considered when interpreting its results. Indeed, a sequential study design was preferred to primarily verify the feasibility of the IVC-IAGP stimulation and to size a suitable control group based on the number of subjects with effective stimulation in the postoperative phase.

Conclusions

A temporary bipolar wire implanted in the IVC-IAGP area allows both standard atrial pacing and epicardial vagal plexus stimulation to be carried out in the first few days after cardiac surgery revascularization. Wire implantation seems feasible, safe, and rapid. Burst IVC-IAGP stimulation significantly attenuated the release of inflammatory cytokines (TNF-α, IL-6, VEGF, and EGF) without significantly influencing serum levels of IL-10 and MCP-1. Larger randomized studies assessing the efficacy of IVC-IAGP stimulation over longer periods of time are warranted in order to extend our results.

Acknowledgments

We thank Tiziana De Santo (Clinical Service Team, Medtronic Italy) for the careful statistical analysis and Prof. Peng-Sheng Chen for his helpful suggestions and for his valuable critical review.

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