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# Multiple Shocks Affect Thoracic Electrical Impedance During External Cardioversion of Atrial Fibrillation

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**Background:** Thoracic impedance (TI) influences the success of external cardioversion (ECV) or defibrillation because current intensity traversing the heart is inversely related to TI. Experimental data suggest that TI decreases after multiple shocks. We undertook a clinical study to determine changes of TI values in patients with atrial fibrillation or flutter requiring ECV.

**Methods:** We enrolled 222 consecutive patients (age  $73 \pm 11$  years; males 67%; body weight  $75 \pm 13$  kg) who underwent ECV between January 2004 and February 2007. Biphasic shocks were delivered through adhesive pads placed in the anteroposterior position. The initial energy was set at 1 J/kg, with progressive increases up to a maximum of 180 J in case of failure. In the last 39 elective patients, plasma concentration of interleukin-6 (IL-6) and tumor necrosis factor (TNF)- $\alpha$  were determined before and 6 hours after ECV.

**Results:** Sinus rhythm was restored in 202 patients (91.0%). Of these, 155 (69.8%) required more than one shock (on average,  $2.5 \pm 1.5$  shocks/patient). Final values of energy and peak current intensity were  $136 \pm 47$  J and  $50 \pm 14$  A, respectively. TI decreased significantly by 6.2% from baseline after  $\geq 2$  shocks ( $P < 0.001$ ). The absolute reduction was correlated with baseline TI, number of delivered shocks, and hemoglobin oxygen saturation. IL-6 and TNF- $\alpha$  increased with ECV ( $P < 0.001$  and  $P = 0.014$ , respectively).

**Conclusions:** TI decreases significantly after multiple shocks, possibly by activation of acute inflammation. (PACE 2009; 32:371–377)

**atrial fibrillation, cardioversion, cytokines, inflammation, thoracic impedance**

## Introduction

The efficacy of external cardioversion (ECV) for atrial fibrillation (AF) and flutter (AFL) is related to the intensity of current traversing the thorax.<sup>1,2</sup> Barring technical factors involving the defibrillator and electrodes, thoracic impedance (TI), an index of electrical resistance, is the most important physical factor conducive to ECV success because it is inversely related to the current amplitude delivered to the heart.<sup>1,2</sup>

Previous studies have investigated TI demonstrating a correlation with body weight, chest size, repeated shocks, size, and contact pressure of paddles.<sup>1,3,4</sup> However, those studies were conducted applying an electrical current to the chest of an-

imal models and humans during the defibrillator charge cycle, before the effective defibrillating shock was delivered, or using special equipments designed for research purposes only.<sup>1,3–6</sup> Recently, we showed that TI in patients undergoing ECV of AF and AFL was directly related to body mass index, female gender, and hemoglobin concentrations, and inversely related to the presence of chronic heart failure (CHF).<sup>7</sup>

TI values might play a significant role in modifying the conceptual approach to defibrillation from an energy-based to a current-based procedure, according to the recommendations contained in the 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care.<sup>8</sup> This switch might encourage clinicians to select more appropriate values of current intensity rather than energy, with the potential of reducing the risk of complications and increasing efficacy.<sup>8</sup> On this basis, we now determined whether multiple shocks, delivered by a defibrillator commonly used in clinical practice, for ECV of AF and AFL, are associated with TI reduction and whether acute inflammation may justify this phenomenon.

Conflicts of interest: none.

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## Methods

### Patients

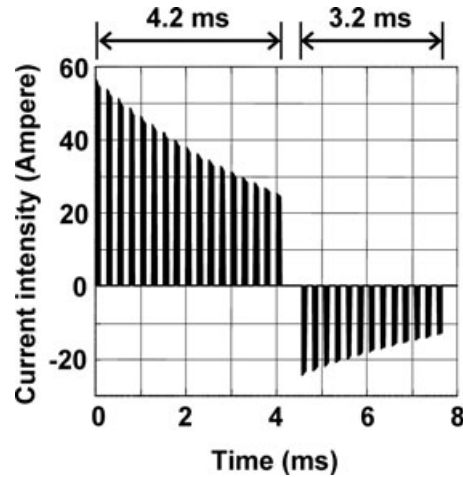
The study consisted of 222 consecutive patients who underwent elective or emergency ECV of AF or AFL, between January 2004 and February 2007. The study was approved by the institutional review committee and all subjects gave informed consent. There were no exclusion criteria. Elective ECV was carried out in patients with persistent or permanent AF after at least 4 weeks of oral anticoagulation therapy with the international normalized ratio (INR) values in the 2–3 range.<sup>9</sup> An echocardiogram was performed in all patients. Routine blood tests, iron balance, erythrocyte sedimentation rate (ESR), C-reactive protein, pro-brain natriuretic peptide level, and hepatic and thyroid function were evaluated in each patient. In the case of hyperthyroidism, ECV was postponed until normalization of thyroid function.

Patients were evaluated according to a protocol based on American College of Cardiology/American Heart Association key data elements and definitions for measuring the clinical management and outcomes of AF.<sup>10</sup> Chronic obstructive pulmonary disease (COPD) and diabetes mellitus were diagnosed using the criteria outlined by the National Heart, Lung, and Blood Institute and World Health Organization<sup>11</sup> and the American Diabetes Association,<sup>12</sup> respectively. The following cardiac diagnoses were considered as possible causes of AF: (1) coronary heart disease (acute/healed myocardial infarction, unstable angina) in the absence of CHF, (2) stage C or D CHF<sup>13</sup> of any etiology, (3) significant valvular dysfunction in the absence of overt CHF,<sup>14,15</sup> (4) hypertension (systolic/diastolic arterial pressure  $\geq 140/90$  mmHg, or antihypertensive therapy),<sup>16</sup> and (5) lone AF in the absence of clinical or echocardiographic evidence of any cardiac disease.

An arterial blood sample was drawn to measure pH, PaO<sub>2</sub>, PaCO<sub>2</sub>, hemoglobin oxygen saturation, and electrolytes immediately before the procedure. Total creatine phosphokinase (CPK), CPK-myocardial band (CPK-MB), myoglobin, and troponin I concentrations were measured at baseline and 6 hours after ECV to estimate cardiac or muscular damage due to the procedure.

### External Cardioversion

ECV was performed under general anesthesia induced through an infusion of sodium thiopental or propofol. Anesthesia lasted about 5 minutes, while maintaining hemoglobin saturation at about 100% with an oxygen mask. ECV was performed using a Defigard 5000 cardioverter/defibrillator (Schiller/ESAOTE, Florence, Italy). Shocks were applied via two oval adhesive pads, 78 cm<sup>2</sup> each,



**Figure 1.** Graphic representation of the multipulse biwave biphasic waveform. The lengths of the positive and the negative components are 4.2 and 3.2 ms, respectively. The waveform is composed by a train of high-frequency isolated impulses separated by pauses. The highest amplitude of the impulse train is the peak current intensity, while the sum of the energies of each impulse is the cumulative energy of the shock.

that were always placed in anteroposterior position.<sup>17,18</sup> The delivered biphasic shock (Multipulse Biwave, Schiller AG, Baar, Switzerland) consisted of a positive and negative component lasting 4.2 and 3.2 ms, respectively, which were separated by a short interval of 0.4 ms, in which no energy was released (Fig. 1). The waveform was not continuous and was composed by a train of isolated impulses generated at high frequency (5,000 Hz), separated by pauses. The highest amplitude of the impulse train was the peak current (A) of the shock, and the sum of the energies of each impulse was the cumulative energy (J) delivered (Fig. 1). The ratio between the length of each segment impulse and the interval to the next one, called the duty cycle, was variable, to dynamically adapt the energy of the shock to the thoracic electrical impedance (ohm), calculated by a microcomputer during the very first part of the shock from the current intensity between the two pads.<sup>19</sup> Compared to other biphasic waveforms, more commonly used in clinical practice, this pulsed waveform has a big advantage: due to the duty cycle, an effective current intensity can be reached with lower cumulative energy levels, minimizing cardioversion side effects. Indeed, the pulse provides a high efficiency, related to the high current intensity, with a reduced risk level, related to the low energy delivered.<sup>19,20</sup>

After each shock, the values of cumulative energy, peak current intensity, and thoracic electrical impedance were recorded. The value of the first

shock of about 1 J/kg of body weight was rounded to the closest multiple of 10. If AF persisted, the energy of the subsequent shocks was increased to 130 and 180 J (maximum energy) for the second and third shock, respectively. If the arrhythmia persisted, two other 180-J shocks were delivered, after which no further attempts were made except in patients not pretreated pharmacologically, in whom two final 180-J shocks were attempted after they were given an intravenous antiarrhythmic agent.<sup>9,21</sup> ECV was considered successful when patients were discharged in sinus rhythm.

### Plasma Concentrations of Inflammatory Cytokines

In the last 39 patients who underwent elective ECV, blood was collected to determine plasma concentrations of interleukin-6 (IL-6) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), at baseline and 6 hours after ECV.

Blood samples were collected in EDTA tubes and centrifuged at 4°C for 15 minutes, at 1000 $\times$ g, within 30 minutes. Plasma was stored at -80°C until IL-6 and TNF- $\alpha$  concentration were measured, using commercially available ELISA kits (UltraSensitive, BioSource International, Camarillo, CA, USA and Quantikine HS, R&D Systems, Abingdon, UK, respectively).

### Statistical Analysis

Data collection and statistical analysis were performed using SPSS for Windows 14.0 (SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as mean  $\pm$  standard deviation, or as median value and range when not normally distributed (Kolmogorov-Smirnov test). Categorical variables are expressed as percentages.

Continuous variables were compared between two or more groups of patients with Student's *t*-test or one-way analysis of variance, respectively, while their correlation was assessed with univariate linear regression analysis. Changes over time were evaluated with general linear models (GLM) for repeated measures, in which we entered all consecutive data for each patient. Nonparametric tests were also used to test variables with large standard deviations. The relation between categorical variables was studied with  $\chi^2$  test.

Bivariate linear regression models or GLM were used to test the association of continuous or categorical clinical variables with changes in TI, while adjusting for baseline TI, which was in fact directly correlated to its variations (see the Results section). To identify the independent predictors of TI changes, variables that were significant at bivariate analysis were then entered into multivariate linear regression models, with backward deletion (*P* out > 0.10).

A *P* value < 0.05 was considered as statistically significant.

## Results

### Patients

Table I outlines the main demographic and clinical characteristics of the 222 patients (190 [85.6%] had AF and 32 [14.4%] AFL). The median AF or AFL duration was 2.5 months (range 1 day to 20 years). Based on arrhythmia duration, patients were stratified into three groups:  $\leq$ 48 hours (16.7%), 48 hours to 6 months (68.1%), and >6 months (15.3%).

Oral anticoagulation was used in 85.4% of patients (Table I). Amiodarone was the single most frequently prescribed antiarrhythmic agent, used in 52.3% of patients before ECV.

### Efficacy of ECV

ECV restored sinus rhythm in 202 of 222 patients (91.0%), with an early, in-hospital relapse occurring in 10 of 202 cases (5.0%). The mean number of shocks and mean final energy were  $2.5 \pm 1.5$  and  $136 \pm 47$  J, respectively. Multiple shocks were used in 155 (69.8%) patients, while a one-shock procedure was effective in the remaining 67 patients. In patients with multiple shocks, the median time interval between the first and the last shock was 2 minutes (range 1–239), and the total delivered energy  $429 \pm 280$  J, corresponding to  $5.7 \pm 3.5$  J/kg of body weight (*P* < 0.001 vs one-shock patients:  $1.2 \pm 0.5$  J/kg of body weight). The related peak current intensity was  $148 \pm 78$  A, corresponding to  $2.0 \pm 1.0$  A/kg of body weight (*P* < 0.001 vs one-shock patients:  $0.5 \pm 0.2$  A/kg of body weight).

Multiple shocks were associated with a significant rise of plasma myoglobin, which was not observed in patients receiving only one shock (>1 shock:  $+50 \pm 132$  ng/mL from baseline vs 1 shock:  $-1 \pm 17$  ng/mL from baseline, *P* < 0.001). Changes in total CPK, CPK-MB, and troponin I were not detected in the two groups of patients.

No ECV-related complications were observed.

### ECV and Thoracic Impedance

Baseline TI was  $57.3 \pm 11.9$  ohm. The use of multiple shocks significantly reduced TI from  $57.7 \pm 11.4$  ohm at first shock to  $54.1 \pm 10.8$  ohm at last shock (*P* < 0.001), with such a reduction occurring in 146 of 155 (94.2%) multiple-shock patients. A retrospective analysis indicated that the power of these observations was >99.9%, with two-tailed  $\alpha = 0.05$ . Multiple, sequential shocks yielded additive effects on TI, which decreased by 6% and 13% from baseline (*P* < 0.001 for both

**Table I**

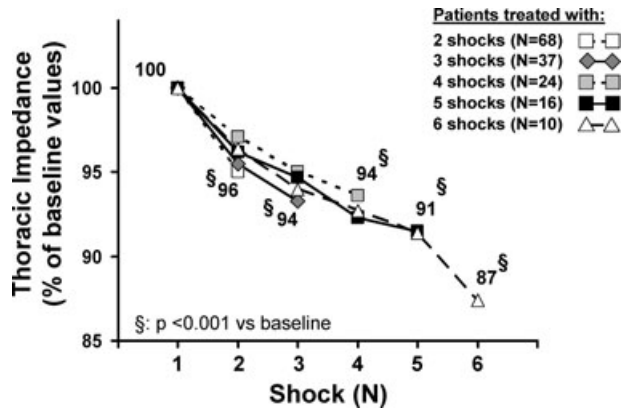
## Demographic and Clinical Characteristics

Variables		Range
Age (years)	73 ± 11	25–95
Males (%)	66.7	
Weight (kg)	75 ± 13	42–120
Height (cm)	169 ± 9	138–192
History of smoking (present/past, %)	54.3	
Comorbid conditions		
Hypertension (%)	77.5	
Chronic heart failure (%)	47.3	
Valvular heart disease		
Aortic (%)	13.1	
Mitral (%)	46.8	
Tricuspid (%)	4.1	
Myocardial infarction (%)	29.7	
History of cardiac surgery (%)	23.0	
Diabetes (%)	16.2	
COPD (%)	9.5	
Echocardiographic data		
LV ejection fraction (%)	48 ± 15	15–72
LAD (mm)	47 ± 6	34–60
LAD > 40 mm (%)	76.2	
Blood tests		
Creatinine (mg/dL)	1.3 ± 0.5	0.7–4.70
Hemoglobin (Hb, g/dL)	13.8 ± 1.6	9.4–17.6
Pro-BNP (pg/mL)	1,596 ± 1499	191–9,435
O <sub>2</sub> Hb saturation (%)	97 ± 2	87–100
TSH (mU/L)	2.79 ± 6.37	0.05–76.00
Drug therapy		
Oral anticoagulation (%)	85.4	
Class I C antiarrhythmic agents (%)	12.1	
β-blocking agents (%)	44.2	
Amiodarone (%)	52.3	
Ca-antagonists (%)	17.1	
Digoxin (%)	45.7	
ACE inhibitors/ anti-ATII (%)	82.4	
Diuretics (%)	52.3	
Statins (%)	24.1	

Abbreviations: COPD = chronic obstructive pulmonary disease; LV = left ventricle; LAD = left atrium diameter; anti-ATII = angiotensin II receptor blockers; BNP = brain natriuretic peptide; ACE = angiotensin-converting enzyme.

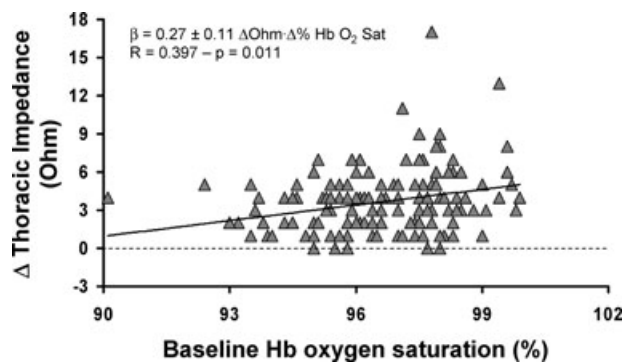
comparisons) after three and six or more shocks, respectively (Fig. 2).

The absolute change in TI was directly correlated to its baseline value ( $\beta \pm SE = 0.08 \pm 0.02$   $\Delta$ ohm for 1 ohm of baseline TI,  $r = 0.348$ ,  $P < 0.001$ ). A bivariate analysis adjusted for baseline



**Figure 2.** Percentage changes of thoracic impedance (TI) during ECV assuming 100% as the starting value. Each line refers to the group of patients treated with the same number of shocks. Each point of every line represents the percentage value of TI observed after the shock indicated on the axis versus the baseline value. For each line the numeric value of last percentage TI is reported. In general linear models for repeated measures the  $P$  values related to each line were all  $<0.001$ .

TI revealed that the maximal reduction in TI was smaller ( $P = 0.033$ ) in the presence of COPD, and greater with increasing hemoglobin oxygen saturation ( $r = 0.397$ ,  $P = 0.011$ ; Fig. 3), number of shocks ( $r = 0.625$ ,  $P < 0.001$ ), time interval between first and last shock ( $r = 0.478$ ,  $P < 0.001$ ), total amount of delivered energy ( $r = 0.564$ ,  $P < 0.001$ ), and total amount of peak current intensity ( $r = 0.597$ ,  $P < 0.001$ ). The length of AF, its cardiac causes, and all the other clinical variables did not show any statistical association with TI reduction. At multivariate analysis after backward deletion of



**Figure 3.** Relationship between hemoglobin oxygen saturation (Hb O<sub>2</sub> Sat) at baseline, before O<sub>2</sub> supplementation, and changes in thoracic impedance (TI) after the last shock. The broken line refers to no variations in TI.  $\beta$ ,  $R$ , and  $P$  values derive from the bivariate model, adjusted for baseline TI.

**Table II**  
Multivariate Predictors of Changes in Transthoracic Impedance

	$\beta \pm SE$	95% CI	P Value
Constant	$-22.42 \pm 8.92$	$-40.05$ to $-4.79$	0.013
Hb O <sub>2</sub> saturation (%)	$0.21 \pm 0.09$	$0.02$ to $0.39$	0.032
Baseline TI (ohm)	$0.06 \pm 0.02$	$0.03$ to $0.09$	<0.001
Number of shock (n)	$0.94 \pm 0.12$	$0.70$ to $1.18$	<0.001

Linear regression analysis;  $r = 0.638$ ,  $P < 0.001$ .

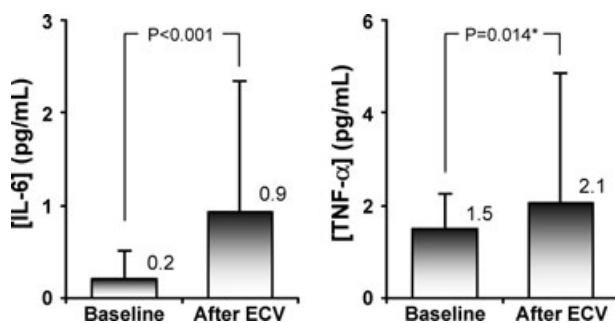
$\beta$  = coefficient of changes in thoracic impedance (dependent variable) for unitary change in independent variable; 95%CI = 95% confidence intervals. Variables backward deleted by the model: COPD ( $P = 0.271$ ); total amount of peak current intensity ( $P = 0.610$ ); time elapsed between the first and the last shock ( $P = 0.111$ ).

COPD ( $P = 0.271$ ), total amount of peak current intensity ( $P = 0.610$ ) and time interval between first and last shock ( $P = 0.111$ ), the reduction in TI correlated directly with baseline TI ( $P < 0.001$ ), number of shocks ( $P < 0.001$ ), and hemoglobin oxygen saturation ( $P = 0.032$ ) (Table II). More in detail, TI decreases of 0.94 ohm for each further shock received by the patient and of 0.21 ohm for each percentage of baseline hemoglobin oxygen saturation.

Changes in TI were still detectable at 239 minutes since the last shock. However, in five patients with early relapse who underwent a second ECV after 24 hours, TI had returned to baseline values (24-hour TI  $56.2 \pm 19.9$  ohm vs baseline TI  $57.4 \pm 22.1$  ohm,  $P = 0.438$ ).

### ECV and Cytokines

Six hours after ECV, mean IL-6 and TNF- $\alpha$  concentrations were markedly increased from normal baseline values (Fig. 4). Such an increase was evident in 66.7% and 75.7% of patients, respectively.



**Figure 4.** Changes of plasma IL-6 and TNF- $\alpha$  concentrations from baseline to 6 hours after external cardioversion (ECV). \* Wilcoxon test P value.

### Discussion

This study demonstrates that multiple electric shocks during ECV induce a significant TI reduction. This phenomenon is linear, implying that the greater the number of shocks, the greater the TI reduction. The decrease of TI is rapidly reversible, as demonstrated in patients who underwent a second ECV 24 hours after the first procedure.

Several factors can influence TI: (1) the dimension, position, and distance between the pads, (2) the chemical characteristics of the gel interfacing with the skin, and (3) the phase of respiration during which the shock occurs.<sup>1-3,22</sup> These variables were always kept constant in our study. In fact, we always used the same type of defibrillator, with preprepped adhesive pads always placed in the anteroposterior position. Finally, respiration should not have affected TI, given that ECV was carried out during apnea after the induction of general anesthesia. Therefore, our data suggest that the TI changes reflect transient modification of tissue conductance. The reproducibility of the observation supports this mechanism because stratifying patients according to the number of shocks yielded parallel TI changes (Fig. 2).

### Factors Influencing Transthoracic Impedance

The multivariate predictors of TI reduction included baseline TI, number of electric shocks, and hemoglobin oxygen saturation. The direct correlation between TI reduction and hemoglobin oxygen saturation might be ascribed, at least in part, to collinearity with COPD, a chronic condition known to affect TI because of reduced muscular mass, increased proportion of fat, and less vascularized lung tissue.<sup>23</sup> Indeed, in our series, COPD patients had a lower reduction of TI than other patients.

IL-6 and TNF- $\alpha$ , two important markers of inflammation, were measured in a limited subset of patients. Both cytokines are able to activate several intracellular pathways, leading to an increase

of acute phase mediators and modulation of vascular permeability.<sup>24</sup> We found a significant ECV-mediated increase in plasma concentrations of IL-6 and TNF- $\alpha$ . These data are particularly relevant because they were collected only for elective ECV, excluding the possible influence of acute diseases on inflammatory markers. IL-6 was under the detectable threshold level at baseline in 84.6% of patients but 6 hours after ECV, its concentration was measurable in 71.8% of patients. Similarly, TNF- $\alpha$  levels increased in 75.7% of patients after ECV. These findings are consistent with the hypothesis that TI decreases after multiple shocks possibly by activation of acute inflammation.

### Limitations

Cytokines were measured only in a relatively small subgroup of patients. The relative skewed distribution of time elapsed between the first and the last shock did not allow us to uncover the full effect of acute inflammation on TI changes. Moreover, the increase of IL-6 concentrations could be dampened by the fact that baseline values of the molecule were under the detectable limit in a majority of subjects.

### Clinical Implications

In the year 2000, the Guidelines on Cardiopulmonary Resuscitation left an unresolved issue, whether or not after an unsuccessful first defibrillation attempt it was necessary to increase the energy level for a second attempt.<sup>2</sup> Two main factors support the proposition of maintaining the same energy level: a statistical consideration regarding the relatively high probability of success of the procedure<sup>2</sup>; alternatively, an increase in transthoracic current intensity mediated by a TI decrease.<sup>1–3</sup> The 2005 Guidelines on Cardiopulmonary Resuscitation overcame, at least in part, this issue, indicating the need to start with the highest possible energy (360 J) with monophasic defibrillators, and with 150–200 J when using

biphasic waveforms.<sup>8</sup> Although this approach will resolve the arrhythmia in more than 90% of patients, there are still about 10% who will need a further shock<sup>8</sup> for whom a decrease in TI may facilitate the restoration of an effective rhythm.

The results of this study support the concept of a shock-related TI reduction.

TI showed a progressive 4% decline after the second attempt, and 9% and 13% decline after the fifth and the sixth attempt, respectively. Even though this result is quantitatively inferior to the 15.8% TI reduction reported by Deakin et al., by applying a 12-kg force to the defibrillator paddles placed in anterolateral position, we must emphasize that only 14% of operators were able to reach this target pressure.<sup>25</sup>

### Conclusion

Multiple shocks for ECV of AF and AFL significantly reduce TI values. Multiple shocks activate acute inflammation with a subsequent increase of vascular permeability and tissue fluid accumulation that might contribute to TI changes. TI decrease is directly related to the number of shocks, as well as the energy and current intensity. In fact, when more than one ECV attempt is necessary, TI reduction may allow a higher and more effective current intensity with a subsequent shock of the same strength. Indeed, the 2000 and 2005 Guidelines on Cardiopulmonary Resuscitation both underscore the importance of TI and encourage a transition from a more generic energy-based to a specific current-based approach for defibrillation and ECV.<sup>2,8</sup> Our results favor this recommendation. Further studies are necessary to better define the role of clinical factors and mediators of acute inflammation on TI variations.

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