CLINICAL RESEARCH

A single pathophysiological pathway in Takotsubo cardiomyopathy: Catecholaminergic stress

Une seule voie physiopathologique à la cardiomyopathie de Takotsubo : le stress catécholaminergique

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KEYWORDS
Takotsubo cardiomyopathy; Pheochromocytoma; Catecholamines

Summary

Background. — Takotsubo cardiomyopathy (TTC) continues to be under-diagnosed, due to its varying presentation, with potentially serious consequences if treatment is delayed.

Aims. — To demonstrate the consistent involvement of catecholaminergic stress in TTC, regardless of the trigger.

Methods. — Between 01 July 2009 and 31 August 2013, patients managed in our centre for thoracic pain syndrome, with or without troponin release, were followed up prospectively.

Abbreviations: β+, β2-mimetic intoxication; CK, creatine kinase; LV, left ventricular; LVEF, left ventricular ejection fraction; PCPG, pheochromocytoma/paraganglioma; TTC, Takotsubo cardiomyopathy.

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Background

Takotsubo cardiomyopathy (TTC) is a rare, but potentially severe, disease [1,2] that was first defined in 1990 [3]. Several retrospective studies have estimated that 0.7–4.9% of patients presenting with suspected acute coronary syndrome have TTC [4], and its incidence is estimated to be 29.8 per 1,000,000 inhabitants in a global population [4,5]. Classically, diagnosis is considered in cases of emotional trauma [3].

The clinical presentation of TTC may mimic acute coronary syndrome, generally involving chest pain, new electrocardiographical abnormalities and biological abnormalities (release of troponin and creatine kinase [CK]) [6]. Imaging (transthoracic echocardiography, left ventricular [LV] angiography or cardiac magnetic resonance imaging) shows transient LV dysfunction; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution (apical ballooning with an octopus trap [Japanese: takotsubo] pattern). Coronary angiography rules out significant coronary artery stenosis [6] and normal LV systolic function is usually recovered within a few weeks [7,8].

The pathophysiology of TTC remains controversial. Epicardial coronary spasm [9–11], atheromatous plaque rupture [12], myocarditis [13] or infarction with healthy coronaries [14] have been suggested, but are now dismissed...

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[15]. Catecholaminergic stress following emotional trauma is presently the hypothesis of choice [9,16]. However, the current Mayo Clinic criteria [6] require catecholamine-secreting tumour to be ruled out for a diagnosis of TTC.

The aim of the present study was to demonstrate the major involvement of catecholaminergic stress in TTC induced by different triggers.

Methods

Between 01 July 2009 and 31 August 2013, patients managed in our centre for chest pain syndrome and/or troponin release were followed up. TTC was diagnosed exclusively from an LV angiographical or echocardiographical pattern of apical (typical TTC) or medial or basal ballooning [17] (medial or inverse TTC) [6] without significant coronary lesions on angiography. Left ventricular ejection fraction (LVEF) was measured on LV angiography (Axiom Sensis XP; Siemens, Erlangen, Germany) and/or echocardiography using the Simpson biplane method (Vivid E9; GE-Vingmed, Horten, Norway). Two experienced blinded operators analysed segmental kinetics retrospectively from DICOM recordings.

Data were collected on history, cardiovascular risk factors and context of onset (emotional trauma, surgical stress or β2-mimetic intoxication [β+]).

From 01 September 2011, all patients (19/40) underwent complementary screening for catecholamine-secreting tumour (pheochromocytoma/paraganglioma [PCPG]) by urinary methoxylate-derivative high-performance liquid chromatography assay (Chromsystems GmbH, Munich, Germany) within the first 3 days and thoracic-abdominal-pelvic computed tomography or methoxy-isobutylisonitrile scintigraphy. Three measurements of 24-hour urinary methoxylate-derivative concentrations were taken during the first 3 consecutive days after admission.

The characteristics of the overall population and various groups were studied according to trigger mechanism: emotional trauma, surgical stress, PCPG or β+. Clinical follow-up comprised functional and therapeutic assessment at 1, 3 and 12 months.

LVEF was assessed by echocardiography and/or LV angiography at initial assessment, and by echocardiography at 7 days, 1 month and 12 months after onset. Troponin and CK concentrations were measured during the initial hospital stay at several time points after TTC onset (6, 12, 24, 48 and 72 hours). Only peak CK and troponin concentrations are presented.

Statistical analysis

Statistical analysis was performed using Stata software, version 12 (StataCorp, College Station, TX, US). The tests were two-sided, with a type I error set at $\alpha = 0.05$. Baseline characteristics are presented as the mean ± standard deviation or median (interquartile range) for each group for continuous data and as the number of patients and associated percentages for categorical variables. These variables were compared between groups using the Chi² or Fisher’s exact test for categorical variables and Student’s t-test or the Mann–Whitney test for quantitative variables, with normality verified by the Shapiro–Wilk test and homoscedasticity by the Fisher–Snedecor test. Owing to sample size, non-parametric tests were often preferred. Considering the sample size and univariate results, no multivariable analysis was considered. Finally, to study the evolution of variables at several time points, mixed models, taking into account within and between subject variability, were considered.

Results

Study population characteristics

Between 01 July 2009 and 31 August 2013, 2754 patients were admitted to our centre for chest pain, with or without troponin release. A diagnosis of TTC was confirmed in 40 patients (40/2754, 1.5%; Fig. 1). Medical care was initiated at a mean of 9.8 ± 6.2 hours after symptom onset.

History-taking found acute adrenergic stress concomitant with symptom onset: emotional trauma (29/40, 72.5%): including family death (11/29, 37.9%) and physical aggression (3/29, 10.3%), surgery (5/40, 12.5%: two ears, nose and throat/bronchopulmonary carcinoma resections, one laparoscopic hernia operation, one carotid endarterectomy and one kidney transplant) and adrenergic intoxication (3/40, 7.5%: two overdoses of β2-mimetics for acute asthma and one voluntary intoxication by intravenous adrenalin injection). These last three patients (adrenergic intoxication) were female (aged 27, 60 and 66 years, respectively), with a cardiogenic shock presentation for the youngest (voluntary intoxication by intravenous adrenalin injection). Interestingly, in three (7.5%) patients, elevated urinary methoxylate-derivative concentrations enabled the diagnosis of a catecholamine-secreting tumour (one paraganglioma and two pheochromocytomas) leading to TTC, confirmed by thoracic-abdominal-pelvic computed tomography or methoxy-isobutylisonitrile scintigraphy. These three patients (two women and one man, aged 65, 50 and 41 years, respectively) did not exhibit any symptoms of catecholamine-secreting tumour (no hypertension, headaches or palpitations) before the diagnosis of TTC.

Patients with TTC due to emotional trauma were older (68.9 ± 11.7 vs 58.5 ± 14.4 years; $P = 0.05$) and more women (29/29 [100%] vs 6/11 [54.5%]; $P = 0.001$) compared with patients in the three other groups (surgery, β+ and PCPG). TTC characteristics are shown in Table 1.

Two cases were of recurrence (one emotional trauma and one PCPG), at intervals of 3 months and 4 years, respectively, after complete recovery.

There were immediate non-specific electrocardiographical abnormalities in 27 (67.5%) patients: ST-segment and T-wave abnormalities and presence of Q wave; the other 13 patients had normal electrocardiograms.

Biological characteristics

We observed increased peak concentrations of CK and troponin in all patients (40/40). The mean troponin I peak concentration was 3.89 ± 6.1 μg/L (range 0.071–30.5 μg/L [normal range 0.015–0.045 μg/L]) and mean CK peak concentration was 687.3 ± 1587.0 μg/L (range 96–6461 μg/L [normal range 39–308 μg/L]).
Nineteen patients had urinary methoxylate-derivative screening. The mean urinary metanephrine concentration was $2.28 \pm 8.29 \mu\text{mol}/24\text{ hours}$ (emotional trauma $0.32 \pm 1.7 \mu\text{mol}/24\text{ hours}$; surgical stress $0.65 \pm 0.56 \mu\text{mol}/24\text{ hours}$; $\beta$+ $0.41 \pm 0.25 \mu\text{mol}/24\text{ hours}$; PCPG $15.07 \pm 19.8 \mu\text{mol}/24\text{ hours}$) (normal range $<4.4 \mu\text{mol}/24\text{ hours}$).

The mean urinary normetanephrine concentration was $2.40 \pm 3.55 \mu\text{mol}/24\text{ hours}$ (emotional trauma $1.63 \pm 0.8 \mu\text{mol}/24\text{ hours}$; surgical stress $2.66 \pm 0.73 \mu\text{mol}/24\text{ hours}$; $\beta$+ $1.62 \pm 0.54 \mu\text{mol}/24\text{ hours}$; PCPG $7.03 \pm 8.9 \mu\text{mol}/24\text{ hours}$) (normal range $<2.2 \mu\text{mol}/24\text{ hours}$).

The mean total urinary metanephrine concentration was $4.68 \pm 11.69 \mu\text{mol}/24\text{ hours}$ (emotional trauma $1.95 \pm 0.93 \mu\text{mol}/24\text{ hours}$; surgical stress $3.31 \pm 1.28 \mu\text{mol}/24\text{ hours}$; $\beta$+ $2.04 \pm 0.63 \mu\text{mol}/24\text{ hours}$; PCPG $22.1 \pm 28.4 \mu\text{mol}/24\text{ hours}$) (normal range $<5.5 \mu\text{mol}/24\text{ hours}$) (Fig. 2).

The mean urinary concentrations of metanephrine, normetanephrine and total metanephrine were higher in the PCPG group than in the other groups (emotional trauma, surgery and $\beta$+) ($P < 0.05$).

**Imaging characteristics**

Imaging (echocardiography [35/40, 87.5%] and/or LV angiography [15/40, 37.4%]) was performed in the cardiological care unit within 3 hours of admission in all patients. Coronary artery angiography ($n = 40$, 100%) found no significant lesions.

Evolutions of mean LVEF are presented in Table 2. Most patients ($n = 35$, 80.0%) presented with a typical TTC pattern (Fig. 3) [6]. The five atypical forms (four medial and one inverse TTC) were all secondary to emotional trauma. All the
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Table 1  Population characteristics.

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 40; 100%)</th>
<th>Emotional trauma (n = 29; 72.5%)</th>
<th>Surgical stress (n = 5; 12.5%)</th>
<th>β+ (n = 3; 7.5%)</th>
<th>PCPG (n = 3; 7.5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>65.0 ± 13.0</td>
<td>67 ± 11.9</td>
<td>63.5 ± 1.7</td>
<td>51 ± 21</td>
<td>56.5 ± 9.2</td>
</tr>
<tr>
<td>Men/women (n/n) CVRFs</td>
<td>6/34</td>
<td>0/29</td>
<td>4/1</td>
<td>0/3</td>
<td>2/1</td>
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<tr>
<td>Hypertension</td>
<td>17 (42.5)</td>
<td>14 (48.3)</td>
<td>2 (40.0)</td>
<td>0</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Smoking</td>
<td>12 (30.0)</td>
<td>8 (27.6)</td>
<td>2 (40.0)</td>
<td>1 (33.3)</td>
<td>1 (33.3)</td>
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<tr>
<td>Diabetes</td>
<td>3 (7.5)</td>
<td>3 (10.3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Dyslipidaemia</td>
<td>6 (15.0)</td>
<td>5 (17.4)</td>
<td>1 (20.0)</td>
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</tr>
<tr>
<td>Familial history of CAD</td>
<td>5 (12.5)</td>
<td>4 (13.8)</td>
<td>0</td>
<td>0</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Overweight (BMI &gt; 25 kg/m²)</td>
<td>8 (20.0)</td>
<td>7 (24.1)</td>
<td>0</td>
<td>1 (33.3)</td>
<td>0</td>
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<tr>
<td>Previous treatment</td>
<td></td>
<td></td>
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<tr>
<td>Beta-blockers</td>
<td>5 (12.5)</td>
<td>5 (17.5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CCBs</td>
<td>7 (17.5)</td>
<td>4 (13.8)</td>
<td>2 (40.0)</td>
<td>1 (33.3)</td>
<td>0</td>
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<tr>
<td>ACEIs</td>
<td>3 (7.5)</td>
<td>3 (10.3)</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>Clinical presentation</td>
<td></td>
<td></td>
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<tr>
<td>Chest pain</td>
<td>28 (70.0)</td>
<td>25 (86.2)</td>
<td>0</td>
<td>2 (66.7)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>APO</td>
<td>4 (10.0)</td>
<td>4 (10.0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>8 (20.0)</td>
<td>1 (3.4)</td>
<td>5 (100)</td>
<td>1 (33.3)</td>
<td>1 (33.3)</td>
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<tr>
<td>History of TTC</td>
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<td>Forms of TTC (n)</td>
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<tr>
<td>Typical</td>
<td>35</td>
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<td>5</td>
<td>3</td>
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<td>Median</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Inverse</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation or number (%), unless otherwise indicated. ACEI: angiotensin-converting enzyme inhibitor; APO: acute pulmonary oedema; β+: β-mimetic intoxication; BMI: body mass index; CAD: coronary artery disease; CCB: calcium channel blockers; CVRF: cardiovascular risk factor; F: female; M: male; PCPG: pheochromocytoma/paraganglioma; TTC: Takotsubo cardiomyopathy.

perioperative, β+-related and PCPG-related forms showed a typical TTC pattern. There was no difference in imaging TTC presentation between emotional trauma patients and other patients (P = 0.20); however, emotional trauma patients presented with a higher initial LVEF than other patients (42 ± 14 vs 29 ± 17; P = 0.01).

One emotional trauma patient experienced recurrence of TTC during follow-up: the primary episode was typical TTC, with complete recovery and the second was inverse TTC.

In-hospital management

Nine (22.5%) patients required vasopressor amine support: adrenaline (n = 1, 2.5%); milrinone (n = 1, 2.5%); noradrenaline (n = 7), 17.5%; dobutamine (n = 4, 10.0%). Four patients (10.0%) required mechanically assisted circulation with extracorporeal membrane oxygenation for a mean of 3 ± 2 days. Invasive mechanical ventilation was implemented in four patients (10.0%) for a mean of 7 ± 2 days. During

Table 2  Left ventricular ejection fraction follow-up of patients presenting with Takotsubo cardiomyopathy.

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 40)</th>
<th>Emotional trauma (n = 29)</th>
<th>Surgical stress (n = 5)</th>
<th>β+ (n = 3)</th>
<th>PCPG (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial LVEF (%)</td>
<td>38.0 ± 15.7</td>
<td>40.1 ± 13.5</td>
<td>15.0 ± 5</td>
<td>52.0 ± 18.2</td>
<td>29.5 ± 0.7</td>
</tr>
<tr>
<td>LVEF at 7 days (%)</td>
<td>55.9 ± 10.7</td>
<td>53.6 ± 11.1</td>
<td>56.0 ± 1.73</td>
<td>70.3 ± 4.0</td>
<td>55.0 ± 3.5</td>
</tr>
<tr>
<td>LVEF at 1 month (%)</td>
<td>57.3 ± 3.7</td>
<td>57.4 ± 4.14</td>
<td>57.4 ± 2.7</td>
<td>56.0 ± 0.3</td>
<td>55.0 ± 0.7</td>
</tr>
<tr>
<td>LVEF at 1 year (%)</td>
<td>59.3 ± 3.6</td>
<td>60.2 ± 4.1</td>
<td>56.5 ± 2.1</td>
<td>58.3 ± 2.9</td>
<td>61.5 ± 9.2</td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation. β+: β-mimetic intoxication; LVEF: left ventricular ejection fraction; PCPG: pheochromocytoma/paraganglioma.
the first 48 hours, angiotensin-converting enzyme inhibitors were prescribed in 23 (57.5%) cases, β-blockers in 13 (32.5%) cases and α-blockers in three (7.5%) cases. The mean stay in the cardiological care unit was 7.1 ± 6.7 days.

**Evolution**

Haemodynamic evolution was favourable in all cases. LVEF improved as of day 7 (Table 2).

However, three (7.5%) patients in the surgical stress group died (D8, D17, D22) of surgery or intensive care complications (nosocomial infections for two patients and invasive mechanical ventilation complication for one patient) after complete recovery of LVEF (> 55%). There was no difference in terms of LVEF between emotional trauma patients and other patients at month 1 (57 ± 4 vs 57 ± 2; P = 0.62) and month 12 (59 ± 8 vs 60 ± 6; P = 0.46).

After a mean follow-up of 23 ± 15 months, 37/40 (92.5%) patients were alive and free of symptoms, with a mean LVEF of 59.3 ± 3.6%. Most surviving patients (n = 35, 94.6%) showed normal LV systolic function (LVEF > 55%) at discharge; 36 (97.3%) showed normal LV systolic function by 1 month.

**Discussion**

The pathophysiology of TTC has been controversial ever since the disease was first described [10] but is steadily becoming less so. Several authors have agreed on the hypothesis of catecholaminergic stress inducing acute LV dysfunction [13,18,19], which has been shown by the present study to be consistently involved in varying clinical situations (Fig. 4).

Previous pathophysiological hypotheses have been ruled out by the most recent findings. The hypothesis of myocarditis was ruled out by myocardial biopsy results and was further confirmed by more recent magnetic resonance...
imaging findings of no signs of myocarditis [20]. The hypothesis of epicardial coronary spasm was put forward [10], but ergonovine-induced spasm tests proved positive in only 14% of cases in the study by Abe et al. [9]. The hypothesis of healthy coronary infarction was soon abandoned [12], as evolution tends toward complete recovery of LV function, without myocardial necrotic sequelae on echocardiography or cardiac magnetic resonance imaging.

The involvement of the adrenergic cascade is presently the hypothesis of choice [13]: physical or emotional stress inundates myocardial β-receptors, stunning the left ventricle. Blood catecholamine concentrations are higher in TTC patients than in Killip class III myocardial infarction patients [21]. Anatomopathological biopsy finds disorganized cell architecture (hypertrophied myocytes, intracytoplasmic areas filled with glycogen, reduced amount of contractile protein actin) without apoptosis [21]. The distribution of myocardial β receptors [22] (a majority of β2 receptors at the apex, with a negative inotropic effect; a majority of norepinephrine-sensitive β1 receptors in basal segments, with a positive inotropic effect) suggests the consistent involvement of catecholaminergic stress, whatever the initial trigger.

Various causes of endogenous or exogenous stress (epileptic seizure [23], surgery [24], meningeal haemorrhage [25,26], synephrine dietary supplements [27], hanging [28] and severe emotional stress [6]) or massive consumption of β2-mimetics saturate myocardial β2 receptors, stunning affected segments and inducing myocardial stunning that is relieved by clearance of the sympathetic receptors. Underlying all these situations is thus sudden major endogenous or exogenous catecholaminergic stress [29].

Studies are presently underway to analyse patients’ genetic predisposition to TTC, in terms of allele variability and gene expression of catecholaminergic pathway receptors, regulators and transducers (TAKOGENE study, NCT01520610).

Although presentation may be extremely serious, haemodynamic prognosis is favourable overall [6]. In the present cohort, there were no deaths due to LV systolic dysfunction and LVEF recovered completely (> 55%) in 94.6% of surviving patients by discharge and in 97.3% by 1 month.

Vasopressor amine support in our study was used before TTC diagnoses were made in a cardiogenic shock situation in the majority of cases. After TTC diagnoses were made, vasopressor amine support was stopped, which may explain the total recovery of this population. Some of these presentations may lead to misdiagnosis, especially in the surgical situation [30], where onset of haemodynamic instability primarily suggests anaphylactic shock. Failure to obtain rapid response to vasopressors is an indication for perioperative echocardiography. Adrenergic drugs, however, could aggravate stunning if TTC has not been diagnosed.

Medical management of the subacute phase relies on β-receptor blockers to maximize relief of adrenergic stress in the affected myocardial segments, but also on angiotensin-converting enzyme inhibitors to enhance LV recovery. Given the risk of recurrence, however low (2/40 [5%] cases in the present series), long-course β-blockers should be considered.

Even in cases of identifiable exogenous stress, catecholamine-secreting tumour should be screened for. Indeed, pheochromocytoma and paraganglioma have an estimated incidence of 10 per million in the general population [31]. However, the present study confirmed that the incidence is significantly higher in patients with TTC (7.5%), as described in some case reports [32]. In the present cohort, a pheochromocytoma was discovered in a patient presenting with TTC following emotional shock (her husband’s funeral). A simple urinary metanephrine-derivative assay can detect most actively-secreting catecholaminergic tumours [33], as we demonstrated that the concentrations were higher in such patients compared with in other groups.

Study limitations

The limitations of the present study should be noted. The sample only comprised 40 patients, although the incidence was similar to that in previous reports [6], and this was one of the largest prospective series published for an entity that is still recent. The favourable spontaneous evolution of minor forms suggests that some cases may be undiagnosed, especially in perioperative situations. Conversely, over the study period, the frequent use of the troponin assay and systematic very early coronary artery and LV angiography in case of myocardial infarction with non-ST segment elevation corrected such underestimation. We did not perform any measurements of urinary metanephrin and normetanephrin concentrations in patients managed in our intensive care unit for chest pain without TTC, although several studies have evaluated this point, with several discrepancies [21,34,35]. Finally, owing to the sample size, a lack of power had to be conceded for statistical analysis.

Conclusions

The acute left ventricular systolic dysfunction characterizing TTC consistently involved myocardial catecholaminergic stress, regardless of the underlying mechanism. Although emotional shock is classically involved, it is essential to rule out catecholamine-secreting tumour (pheochromocytoma, paraganglioma). Haemodynamic instability in the perioperative period or in patients treated with β2-mimetics may also suggest TTC. The demonstration of this single pathophysiological mechanism should allow early diagnosis and adapted treatment, usually enabling complete recovery of LV function.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Acknowledgments

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