Single-wire pressure and flow velocity measurement for quantifying microvascular dysfunction in patients with coronary vasospastic angina

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Yamanaga K, Tsujita K, Komura N, Kaikita K, Sakamoto K, Miyazaki T, Saito M, Ishii M, Tabata N, Akasaka T, Sato K, Horio E, Arima Y, Kojima S, Tayama S, Nakamura S, Hokimoto S, Ogawa H. Single-wire pressure and flow velocity measurement for quantifying microvascular dysfunction in patients with coronary vasospastic angina. Am J Physiol Heart Circ Physiol 308: H478–H484, 2015. First published December 19, 2014; doi:10.1152/ajpheart.00593.2014.—Endothelial and vascular smooth muscle dysfunction of epicardial coronary arteries play a pivotal role in the pathogenesis of vasospastic angina (VSA). However, coronary microvascular (MV) function in patients with VSA is not fully understood. In the present study, subjects without coronary obstruction were divided into two groups according to the acetylcholine provocation test: VSA group (n = 29) and non-VSA group (n = 21). Hyperemic MV resistance (hMR) was measured using a dual-sensor (Doppler velocity and pressure)-equipped guidewire, and guidewire-derived hemodynamic parameters were compared. There were no between-group differences in clinical demographics, including potential factors affecting MV function (e.g., diabetes). Although coronary flow velocity reserve was similar between the two groups [2.4 ± 1.0 (VSA group) vs. 2.4 ± 0.9 (non-VSA group); P = 0.8], coronary vessel resistance and hMR were significantly elevated in the VSA group compared with the non-VSA group (2.6 ± 3.1 vs. 1.2 ± 0.8, P = 0.04; 1.9 ± 0.6 vs. 1.6 ± 0.5, P = 0.03, respectively). Coronary vasospasm, older age, E/e', and estimated glomerular filtration rate were significantly associated with MV dysfunction [defined as ≥ median value of hMR (1.6)] in univariate analysis. Coronary vasospasm most strongly predicted higher hMR in multivariate logistic regression analysis (odds ratio, 4.61; 95% confidence interval, 0.98–21.60; P = 0.053). In conclusion, coronary MV resistance is impaired in patients with VSA compared with non-VSA patients, whereas coronary flow velocity reserve is maintained at normal levels in both groups. In vivo assessment of hMR might be a promising index of coronary MV dysfunction in patients with VSA.

Coronary MV function in various cardiovascular diseases, such as coronary syndrome X or Takotsubo cardiomyopathy, has been recently determined (10, 13). However, coronary MV function in patients with coronary vasospastic angina (VSA) is not well known. When coronary flow velocity reserve (CFVR) was used, conflicting results have been reported regarding the presence or absence of MV dysfunction in patients with VSA (1, 20). CFVR is affected by baseline hemodynamic changes because of the resting parameter included in its formula. Direct coronary MV resistance measurements, such as the index of MV resistance (IMR) or hyperemic MV resistance (hMR), are newly developed, specific, quantitative indexes of coronary MV function. These methods have provided further insight into the physiological aspect of cardiovascular diseases. When coronary arterial distal pressure (Pd) and average peak velocity (APV) are measured at hyperemia using a dual-sensor (Doppler velocity and pressure)-equipped guidewire, hMR is calculated as Pd/APV from the law of Ohm (12, 14, 22).

In this study, we used dual-sensor-equipped guidewire-derived hemodynamic parameters and analyzed the coronary arterial responses to intracoronary administration of ACh and at the time of a hyperemic state in patients with VSA.

MATERIALS AND METHODS

Study patients. We recruited stable patients with suspected angina who were admitted to Kumamoto University Hospital from June 2011 to October 2014 (Fig. 1). During this period, 186 patients underwent the ACh provocation test for evaluation of chest symptoms. Hemodynamic parameters of the coronary circulation were quantitated by using a 0.014-inch guidewire, which was equipped with a Doppler velocity probe and a pressure sensor (Combowire, Volcano, San Diego, CA). We excluded 136 patients with possible heart failure (ejection fraction <50%) or obstructive coronary artery disease (>50% diameter or previous history of coronary intervention). Finally, 50 patients with angina-like chest symptoms and without possible heart failure or obstructive coronary artery disease, who completed the ACh provocation test, were enrolled in the current study. Among them, based on the Japanese Circulation Society’s guideline for VSA (6), 29 patients were positive for the ACh provocation test (VSA group) and the remaining 21 patients were negative (non-VSA group). For comparison of hemodynamic indexes of coronary function as measured by the Combowire, we quantitatively evaluated MV function in patients with VSA.

Patients’ demographics, including parameters of ultrasound cardiography, were confirmed by hospital chart review at the time of the procedure. Coronary risk factors included diabetes mellitus (diet controlled, oral agent, or insulin treated), hypertension (treated by medication only), cigarette smoking, and a family history of coronary artery disease. Written, informed consent was obtained from each

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patient before coronary angiography (CAG) and a comprehensive
diagnostic analysis. This study was approved by the ethics committee
of our institution and fully complied with the Declaration of Helsinki.

**ACh provocation test and decision criteria.** All vasoactive drugs,
including calcium channel blockers, nitrates, and nicorandil, were
discontinued ≥72 h before the ACh test. We performed all of the
examinations in the morning during fasting. After right heart cathe-
terization and baseline CAG without intracoronary isosorbide dini-
trate (ISDN) administration, we inserted the Combowire into the left
anterior descending coronary artery (LAD). Incremental doses (20,
50, and 100 µg) of ACh chloride were injected into the left coronary
artery over a period of 30 s each, and CAG was performed 1 min after
the start of each provocation. The doses of ACh were administered at
4-min intervals. Subsequently, 50 µg of ACh was injected into the
right coronary artery without the Combowire, and CAG was per-
formed. VSA was defined as transient, total, or subtotal occlusion (>90% stenosis) of a coronary artery with signs/symptoms of myo-
cardial ischemia (angina pain and ischemic ST changes), as de-
scribed by the Japanese Circulation Society’s guideline of va-
sospastic angina (6). Therefore, the patients in the VSA group of
our study are considered to have definite VSA of the guidelines.

After the ACh provocation test, ISDN was injected into the left and
right coronary arteries, and post-ISDN coronary angiography was
performed (Fig. 2).

**Quantitative CAG.** The diameter of the lumen of the LAD at end
diastole where the tip of the Combowire was present was measured
with a computer-assisted coronary angiographic analysis system
(CAAS 5.7 version 5.7.0; Pie Medical Imaging, Maastricht, The
Netherlands) by calibrating the measurement with a 6-Fr guiding
catheter. The coronary artery diameter was measured by two blinded
investigators (K.Y. and K.T.) at four time points: baseline and after
each ACh provocation (20, 50, and 100 µg).

**Hyperemic MV resistance measurements.** After administration of
intracoronary ISDN and post-ISDN CAG, the Combowire was in-
serted into the proximal site of the LAD and adenosine triphosphate
(ATP; 150 µg·kg⁻¹·min⁻¹) was administered via the central vein
until maximal hyperemia was achieved for the calculation of hemo-
dynamic parameters. Aortic pressure (Pa) was measured via a guiding
catheter that was placed at the left coronary ostium. Mean Pd and
APV were measured using dual sensors of the Combowire. Fractional
flow reserve (FFR), CFVR, hyperemic stenosis resistance, and hMR
were measured as described previously at the time of coronary
maximal hyperemia (Fig. 2) (14). Coronary blood flow (CBF) during
ATP administration could not be calculated because CAG was not
performed at that time and the vessel diameter where the tip of the
Combowire was located could not be measured. Therefore, we only
calculated hMR in this condition.

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**Patient Flow Chart**

- 186 pts. underwent ACh provocation test
- 50 pts. enrolled in the current analysis
- 29 pts. positive for ACh provocation test (VSA group)
- 21 pts. negative for ACh provocation test (Non VSA group)
- 136 pts. excluded
  - 123 pts. with coronary obstruction (>50%) or previous history of coronary intervention.
  - 13 pts. with possible heart failure (ejection fraction <50%)

**Study Flow Chart of ACh Provocation Test**

- Resting state
  - Right heart catheterization
  - Pre-ISDN Control CAG
- ACh test
  - LAD: 20µg/50µg/100µg
  - RCA: 50µg
- Post-ISDN CAG
- Hemodynamic measurement with ATP

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Fig. 1. Flow chart of the patients’ recruitment. VSA, vasospastic angina; pts, patients.

Fig. 2. Flow chart of the ACh provocation test. ISDN, isosorbide dinitrate; CAG, coronary angiography; LAD, left anterior descending coronary artery; RCA, right coronary artery.

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CBF and coronary vascular resistance measurements during the ACh provocation test. Mean Pd and APV were measured by the Combowire at each time that the ACh provocation test was performed and CAG was also performed. CBF of the proximal LAD was quantitatively calculated as reported previously (3): 

\[ CBF = \frac{\pi \times (ACh/2) \times \text{vessel diameter}/2}{2} \]

We also calculated coronary vascular resistance (CVR) as the ratio of mean Pd to CBF from the law of Ohm (5). Using CVR, we could analyze coronary arterial resistance during the ACh provocation test, even if vessel diameters were changed. A newly generated ACh-provoked vasomotor response variable was defined as the reciprocal of CVR at ACh 100 μg provocation divided by the reciprocal of CVR at resting state (before ACh provocation) to evaluate endothelial function of the coronary artery.

Statistical analysis. Statistical analysis was performed with SPSS version 22.0 software (SPSS, Chicago, IL). Continuous variables (means ± 1 SD) were compared with the unpaired Student’s t-test or Mann-Whitney U test as appropriate, according to the distribution of data. Categorical variables (frequencies) were compared with χ²-statistics or Fisher’s exact test. Logistic regression analysis was used to determine predictors of high hMR (≥median value of hMR). Based on an a priori determination, the univariate variables reached significance were entered into the multivariate analysis. A P value <0.05 was considered significant. Because this study was exploratory, no power analysis or sample size estimate was performed in advance.

RESULTS

Baseline characteristics. The baseline characteristics of the study patients are shown in Table 1. There were no significant differences in age, sex, or other traditional coronary risk factors, including hypertension and diabetes mellitus between the two groups. Reactive hyperemic-peripheral arterial tonometry, which reflects endothelial dysfunction, was impaired in the VSA group compared with the non-VSA group (19.0 ± 0.6 vs. 2.2 ± 0.6; P = 0.1), although the between-group differences did not reach statistical significance.

Hemodynamic characteristics during the ACh provocation test. The hemodynamic response to ACh provocation is shown in Table 2. There were no differences in APD and Pd between the VSA and non-VSA groups. However, CBF at ACh 100 μg provocation was significantly lower and CVR was significantly higher in the VSA group than in the non-VSA group (66.2 ± 39.1 ml/min vs. 120.6 ± 82.0 ml/min, P = 0.02; 2.6 ± 3.1 mmHg·ml⁻¹·min⁻¹ vs. 1.2 ± 0.8 mmHg·ml⁻¹·min⁻¹, P = 0.04). In terms of the association between the impairments of endothelium in the epicardial coronary artery and the abnormality of MV circulation, there was significant negative correlation between the ACh-provoked vasomotor response variable and hMR value (y [vasomotor response variable] = −0.9258x [hMR] + 3.5751, Spearman R = -0.400, P = 0.02).

Hemodynamic characteristics after the ACh provocation test. The parameters of MV function are shown in Table 3. There was no difference in duration from the ACh test (after ACh 100 μg provocation) to ATP administration between the two groups. There were also no between-group differences in MV resistance at the resting state (before ACh administration) and baseline state (before ATP administration). This meant that coronary vasospasm did not remain in the microvasculature after the ACh provocation test and ISDN administration. The ACh provocation test and Combowire-derived hemodynamic parameters could be safely and steadily measured without any procedure-related complications in all of the patients. There was no significant difference in FFR value between the groups. CFVR and FFR/CFVR, which might indicate MV dysfunction if there was no epicardial coronary obstruction, were not different between the two groups. However, hMR-derived MV relaxant properties were significantly impaired in the VSA group compared with the non-VSA group (1.9 ± 0.6 vs. 1.6 ± 0.5, P = 0.03; Table 3 and Fig. 3).

Predictors of high hMR. Logistic regression analysis was used to clarify the predictors of high hMR [hMR ≥1.6 (median value), Table 4]. In univariate analysis, age, E/e′, eGFR, and the presence of coronary vasospasm were potential predictors, regardless of the small number of study patients (odds ratio, 4.61; 95% confidence interval, 0.98–21.60; P = 0.053), although it was not quite significant.

DISCUSSION

The main findings of the present study were as follows: 1) CVR was significantly higher in the VSA group than in the non-VSA group in the ACh provocation test; 2) hyperemic coronary MV resistance was significantly increased in patients

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### Table 1. Clinical characteristics of patients with and without VSA

<table>
<thead>
<tr>
<th></th>
<th>VSA Group</th>
<th>Non-VSA Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>29</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>61.8 ± 10.8</td>
<td>60.7 ± 14.3</td>
<td>0.8</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>14 (48)</td>
<td>12 (57)</td>
<td>0.6</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.3 ± 3.7</td>
<td>22.9 ± 3.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.60 ± 0.20</td>
<td>1.63 ± 0.22</td>
<td>0.7</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>17 (59)</td>
<td>11 (52)</td>
<td>0.7</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>19 (66)</td>
<td>10 (48)</td>
<td>0.2</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>7 (24)</td>
<td>3 (14)</td>
<td>0.4</td>
</tr>
<tr>
<td>Chronic kidney disease, n (%)</td>
<td>6 (21)</td>
<td>3 (14)</td>
<td>0.6</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td>7 (24)</td>
<td>3 (14)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>8 (28)</td>
<td>8 (38)</td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>14 (48)</td>
<td>10 (48)</td>
<td></td>
</tr>
<tr>
<td>Medication, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>10 (28)</td>
<td>6 (29)</td>
<td>0.7</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>3 (10)</td>
<td>3 (14)</td>
<td>0.7</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>14 (48)</td>
<td>11 (52)</td>
<td>0.8</td>
</tr>
<tr>
<td>Nitrate</td>
<td>8 (28)</td>
<td>3 (14)</td>
<td>0.3</td>
</tr>
<tr>
<td>Statin</td>
<td>13 (45)</td>
<td>7 (33)</td>
<td>0.4</td>
</tr>
<tr>
<td>Ultrasound cardiography parameters</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>LV ejection fraction, %</td>
<td>64.8 ± 4.4</td>
<td>64.0 ± 5.7</td>
<td>0.6</td>
</tr>
<tr>
<td>LV end-diastolic diameter, mm</td>
<td>44.3 ± 5.1</td>
<td>44.4 ± 6.0</td>
<td>0.8</td>
</tr>
<tr>
<td>LV end-systolic diameter, mm</td>
<td>26.1 ± 4.2</td>
<td>27.9 ± 5.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Interventricular septal thickness, mm</td>
<td>10.2 ± 2.2</td>
<td>9.5 ± 1.8</td>
<td>0.1</td>
</tr>
<tr>
<td>LV posterior wall thickness, mm</td>
<td>9.7 ± 1.4</td>
<td>9.4 ± 1.6</td>
<td>0.4</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>94.6 ± 28.7</td>
<td>85.8 ± 21.4</td>
<td>0.3</td>
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<tr>
<td>B-type natriuretic peptide, pg/ml</td>
<td>42.2 ± 96.2</td>
<td>18.6 ± 15.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate, ml/min/1.73 m²</td>
<td>70.1 ± 20.4</td>
<td>75.7 ± 17.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Mean pulmonary wedge pressure, mmHg</td>
<td>10.2 ± 5.1</td>
<td>8.1 ± 3.6</td>
<td>0.1</td>
</tr>
<tr>
<td>Reactive hyperemic-peripheral arterial tonometry</td>
<td>1.9 ± 0.6</td>
<td>2.2 ± 0.6</td>
<td>0.1</td>
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</table>

Values are means ± 1 SD or number (%). VSA, vasospastic angina; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; LV, left ventricular.
with VSA compared with non-VSA patients without coronary obstruction, suggesting impaired endothelial-independent MV relaxant function in VSA patients; and 3) except for the presence of VSA, older age, E/e’, and deterioration of eGFR also appeared to be associated with augmented hMR.

Coronary vascular resistance in VSA. When coronary vasospasm occurs, epicardial coronary arteries constrict and CBF is decreased compared with myocardial oxygen demand, causing myocardial ischemia. Many studies (8) have reported angiographic changes (focal and diffuse spastic changes), myocardial lactate production, and decreased CBF, but few studies have reported measuring CVR because of a lack of Pd pressure dial lactate production, and decreased CBF, but few studies have reported measuring CVR because of a lack of Pd pressure.

Mechanisms underlying elevated hMR in VSA. To date, although there is no direct evidence showing pathogenic mechanisms underlying the association between coronary vasospasm and MV dysfunction, several basic and clinical studies have yielded some important possibilities. Previous clinical studies accomplished by our department (15, 21) and others (16) have clearly shown that pathogenic abnormalities that are responsible for coronary vasospasm may not be confined to localized coronary spastic segments. However, these abnormalities may be present in the entire coronary arteries of patients with VSA. These data show that diffuse intimal thickening extends to spastic coronary arteries, at least in epicardial arterial segments that are observable by any clinically available coronary imaging modality (e.g., intravascular ultrasound and/or optical coherent tomography). In addition, a previous study showed that MV dysfunction in patients with arterial hypertension and in spontaneously hypertensive rats was derived from structural remodeling of intramural coronary arterioles (11). Furthermore, our study showed that CVR value was correlated with impaired ACh-provoked vasomotor response, indirectly suggesting the spreading of coronary relaxant impairment and structural remodeling throughout the entire coronary tree rather than confined epicardial coronary segment. Based on these clinical and basic findings, these morphological and structural alterations of the microcirculation (e.g., structural thickening of the intima/media and diffuse luminal narrowing) may provide a potential explanation for elevated hMR in patients with VSA, as shown in our study.

Discrepancies in previously published data regarding CFVR in VSA. Some studies have reported a correlation between VSA and coronary MV dysfunction, but their results are conflicting. Akasaka et al. (1) reported that in diffuse spasm patients, CFVR was lower than in focal spasm patients or nonspasms patients. However, other studies have reported that coronary MV function may be preserved in VSA patients and that there is no correlation between VSA and MV dysfunction (20). A possible explanation for this discrepancy between studies could be that they only used CFVR as a marker of coronary MV dysfunction. Many factors affect coronary MV dysfunction, but CFVR was the only clinically available modality of assessment of coronary MV dysfunction when these previous studies were performed. CFVR is a ratio of coronary blood flow at hyperemia to coronary blood flow at rest. Therefore, many systemic hematological and endocrinological factors (e.g., anemia and hyperthyroidism), which involve the state of coronary spasm and MV dysfunction, several basic and clinical studies have yielded some important possibilities. Previous clinical studies accomplished by our department (15, 21) and others (16) have clearly shown that pathogenic abnormalities that are responsible for coronary vasospasm may not be confined to localized coronary spastic segments. However, these abnormalities may be present in the entire coronary arteries of patients with VSA. These data show that diffuse intimal thickening extends to spastic coronary arteries, at least in epicardial arterial segments that are observable by any clinically available coronary imaging modality (e.g., intravascular ultrasound and/or optical coherent tomography). In addition, a previous study showed that MV dysfunction in patients with arterial hypertension and in spontaneously hypertensive rats was derived from structural remodeling of intramural coronary arterioles (11). Furthermore, our study showed that CVR value was correlated with impaired ACh-provoked vasomotor response, indirectly suggesting the spreading of coronary relaxant impairment and structural remodeling throughout the entire coronary tree rather than confined epicardial coronary segment. Based on these clinical and basic findings, these morphological and structural alterations of the microcirculation (e.g., structural thickening of the intima/media and diffuse luminal narrowing) may provide a potential explanation for elevated hMR in patients with VSA, as shown in our study.

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artery autoregulation, can affect the value of CFVR, increasing coronary blood flow at rest. Conversely, if coronary blood flow at rest is decreased, CFVR is calculated as a high value, and it might be incorrectly recognized as preserved coronary MV function. CVFR is a useful modality, but it reflects one of the aspects of MV function, and is subject to hemodynamic conditions, such as heart rate or blood pressure. Determining MV resistance, such as the index of MV resistance or hMR, is a newly developed method of examining MV dysfunction, and it provides quantitative absolute values. With the use of hMR, absolute values of coronary MV function can be obtained, and it might contribute to better understanding of coronary MV hemodynamic function in various situations.

Clinical implication of MV dysfunction in VSA. Recently, some reports have suggested that impaired coronary reactivity to ACh is an independent predictor of poor prognosis and predicts cardiovascular events in patients with epicardial coronary artery disease (18, 19). Additionally, better coronary MV responses to ACh have been found to be associated with improved survival (4). Abnormal coronary vasoreactivity is believed to be a precursor to atherosclerotic disease (15, 16, 21). Coronary MV dysfunction is correlated with traditional atherosclerotic risk factors (2). These reports suggest that coronary MV dysfunction and VSA are early manifestations of atherosclerosis. We also found that hMR was higher in VSA patients than in non-VSA patients. Our current result might also indirectly provide possible explanation for poor clinical prognosis in patients with positive ACh provocation test.

Study limitations. There are several limitations to this study. First, the study population was relatively small. Second, this was a retrospective single-center study. Third, our study population only included 50 patients, and this number might have been too small to use multivariate analysis. Fourth, there was no direct evidence validating the diagnostic accuracy of hMR as a marker of MV dysfunction in patients without obstructive coronary arteries. Fifth, our current analysis did not include...
prognostic information of the study patients. Sixth, further studies could help elucidate underlying mechanisms of the coronary MV dysfunction in patients with VSA, since our current findings are partly hypothesis generating.

Conclusion

During the ACh provocation test, CVR is significantly higher in VSA patients than in non-VSA patients. With the use of hMR, our study provides the first evidence of increased coronary MV resistance in VSA patients. Higher hMR is associated with age, E/e′, eGFR, and VSA, suggesting the existence of concurrent early atherosclerotic changes in the coronary microcirculation in patients with VSA.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES


