Abstract
Coronary angiograms performed at the time of an acute coronary syndrome typically present vessel occlusions, ruptured plaques or thrombotic lesions that require reperfusion therapy. However, occasionally, no coronary artery stenoses are detected. Myocardial ischemia frequently causes left ventricular wall motion abnormalities that can be seen easily by echocardiography. In our study we aimed to analyze echocardiographic findings in patients with acute coronary syndrome and normal angiogram. After standardized risk stratification, a total of 897 patients were classified as an acute coronary syndrome and underwent a coronary angiography immediately. In 76/897 patients angiography excluded coronary macroangiopathy. Routine echocardiographic assessment in patients with normal angiogram showed in 21.1% a reduced left ventricular systolic function and 32.9% presented with segmental wall motion abnormalities.

In summary, by detection of segmental wall motion abnormalities in 1/3 of patients with suspected acute coronary syndrome and normal angiogram, obviously, an echocardiographic evaluation in this patient population is of clinical relevance. Recommendations for performing echocardiography in patients with suspected acute coronary syndromes independent of angiographic findings are strongly supported. Further analyses should implement echocardiographic techniques as contrast and tissue doppler imaging.

Key words: Echocardiography, acute coronary syndrome, normal angiogram

INTRODUCTION
Acute coronary syndrome comprises different manifestations of coronary artery disease [1]. Angiograms performed at the time of an acute coronary syndrome may present different coronary morphologies. In many cases, there are acute vessel occlusions, ruptured atherosclerotic plaques or thrombotic lesions that require reperfusion therapy. However, occasionally, no coronary artery stenoses are detected. In these cases, different diagnoses may explain the unexpected angiographic findings. For example peri-myocarditis, coronary spasms, muscle bridges, or hypertensive heart disease may mimic the clinical situation of an acute coronary syndrome [2-4]. However, myocardial ischemia may not be detected by coronary angiography in all cases.

Myocardial ischemia frequently causes left ventricular wall motion abnormalities that can be seen easily by echocardiography. Echocardiographic findings precede electrocardiographic abnormalities and angina. Presence and severity of myocardial dysfunction can be documented rapidly, so that echocardiography is an important modality for risk stratification in the emergency room [5-7]. Echocardiography is a useful tool in the prognostic evaluation of myocardial infarction [8]. Left ventricular angiography may not be appropriate in critically ill patients. Therefore, echocardiography is implemented in the guidelines concerning management of patients with acute coronary syndromes [9].

However, which echocardiographic findings can be obtained in patients with acute coronary syndromes but normal angiograms? How many of these patients have wall motion abnormalities? May echocardiography identify patients with different diagnoses requiring further diagnostic procedures or a specific therapy? In our study we aimed to analyze echocardiographic findings in patients with acute coronary syndrome and normal angiogram.

MATERIALS AND METHODS
Between 1996 and 2000, a total of 897 coronary angiographies were performed as an emergency procedure due to suspected acute coronary syndrome in our institution. Acute coronary syndromes were defined according to the standard risk stratification combining electrocardiography (ST-segment elevation >1mm in two or more contiguous leads, ST-segment depression of at least 0.5mm in two or more contiguous leads, T-wave inversion of at least 1mm), elevated troponin T (cTnT; quantitatively >0.1µg/l) and clinical symptoms [1, 10]. However, guideline-oriented risk stratification changed over the period patients were included in this analysis; cTnT could be only determined qualitatively by bed-side test until 1997 and was not available as a routine quantitative marker until 1998 in our institution. Normal coronary arteries were defined as the absence of coronary lesions with diameter stenosis >50% and with a normal perfusion (TIMI III) [11].
Transthoracic echocardiography was performed in patients without coronary artery disease at the day of angiography. Overall ejection fraction was measured by the modified Simpson's method. Left ventricular segmental wall motion was analyzed by B-mode echocardiography according to the 16-segment model [12]. Ultrasound examinations were performed by using a HP SONOS 5500 (Philips, Eindhoven, The Netherlands) by experienced sonographers.

RESULTS

Patient assessment was done by risk stratification and all patients were managed as an acute coronary syndrome. Coronary artery disease was found in 821 patients (91.5%), whereas no coronary artery disease was documented in 76 patients (8.5%) (53±13.9 years, 71.1% male). The group with normal angiogram was characterized as unstable angina without ST-elevation (n = 66, 86.8%) and acute ST-elevation myocardial infarction (n = 10, 13.2%). The patient group with coronary artery disease had unstable angina without ST-elevation (n = 445, 54.2%) and ST-elevation myocardial infarction (n = 376, 45.8%) (Table 1). In this group, mechanical revascularization was performed in 86.3%.

Table 1. Baseline characteristics and risk stratification.

<table>
<thead>
<tr>
<th></th>
<th>No CAD</th>
<th>CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>8.5% (n = 76)</td>
<td>91.5% (n = 821)</td>
</tr>
<tr>
<td>Male</td>
<td>71.1% (n = 54)</td>
<td>73.8% (n = 607)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53±14</td>
<td>62.6±12</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>60.5% (n = 46)</td>
<td>80.3% (n = 659)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>11.8% (n = 9)</td>
<td>27.8% (n = 228)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>67.1% (n = 51)</td>
<td>86.1% (n = 707)</td>
</tr>
<tr>
<td>Smoking</td>
<td>57.8% (n = 44)</td>
<td>69.8% (n = 573)</td>
</tr>
<tr>
<td>Elevated troponin</td>
<td>30.3% (n = 23)</td>
<td>64.3% (n = 528)</td>
</tr>
<tr>
<td>Elevated CK</td>
<td>21.1% (n = 16)</td>
<td>47.9% (n = 393)</td>
</tr>
<tr>
<td>ECG-ischemia/LBBB</td>
<td>57.8% (n = 44)</td>
<td>64.8% (n = 533)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>86.8% (n = 66)</td>
<td>54.2% (n = 445)</td>
</tr>
<tr>
<td>STEMI</td>
<td>13.2% (n = 10)</td>
<td>45.8% (n = 376)</td>
</tr>
</tbody>
</table>

CK = creatine phosphokinase, LBBB = left bundle branch block, STEMI = ST-elevation myocardial infarction

In the group of patients with normal angiogram, troponin was positive in 30.3%, and creatine phosphokinase was elevated in 21.1% prior to angiography. Signs of ischemia in the electrocardiogram had 57.8%. In comparison, 64.8% of the patients with coronary artery disease had signs of ischemia in the electrocardiogram, 64.3% had elevated troponin levels (Table 1).

Prior to angiography, patients in the group with normal angiogram were treated with systemic thrombolysis (n = 6, 7.9%), heparin (n = 67, 88.2%), glycoprotein IIb/IIIa-inhibitors (n = 9, 11.8%), acetylsalicylic acid (n = 56, 73.7%) and thienopyridines (n = 4, 5.3%).

Invasive findings in the group without atherosclerotic coronary artery disease were coronary spasms (n = 5, 6.6%), and muscle bridges (n = 4, 5.3%). Complete diagnostic evaluation revealed cardiomyopathy (n = 2, 2.6%), hypertensive heart disease (n = 11, 14.5%), and peri-/myocarditis (n = 8, 10.5%). No specific diagnosis could be attributed to 46 patients (60.5%) (Table 2).

Table 2. Diagnoses.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>No coronary artery disease</td>
<td>76</td>
<td>100%</td>
</tr>
<tr>
<td>No specific findings</td>
<td>46</td>
<td>60.5%</td>
</tr>
<tr>
<td>Coronary spasm</td>
<td>5</td>
<td>6.6%</td>
</tr>
<tr>
<td>Muscle bridge</td>
<td>4</td>
<td>5.3%</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>2</td>
<td>2.6%</td>
</tr>
<tr>
<td>Hypertensive heart disease</td>
<td>11</td>
<td>14.5%</td>
</tr>
<tr>
<td>Peri-/Myocarditis</td>
<td>8</td>
<td>10.5%</td>
</tr>
</tbody>
</table>

In the majority of patients with normal angiogram echocardiography obtained a normal left ventricular ejection fraction (Table 3). A moderate reduced ejection fraction had 15.8% of patients, whereas 5.3% presented with an ejection fraction lower than 40%. Analyzing the segmental wall motion behaviour, 67.1% patients showed a normal contractility. Echocardiography documented wall motion abnormalities in inferior (14.5%), anterior (11.8%) and septal regions (6.6%). No pericardial effusion was documented, no case of apical ballooning. Due to the limited number of patients, there was no association between angiographic and echocardiographic findings of segmental wall motion abnormalities.

Table 3. Echocardiographic findings in patients with normal angiogram.

<table>
<thead>
<tr>
<th>Wall motion</th>
<th>n</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF &gt;60%</td>
<td>78.9%</td>
<td>(n = 60)</td>
</tr>
<tr>
<td>EF 40-60%</td>
<td>15.8%</td>
<td>(n = 12)</td>
</tr>
<tr>
<td>EF &lt;40%</td>
<td>5.3%</td>
<td>(n = 4)</td>
</tr>
<tr>
<td>Normal wall motion</td>
<td>67.1%</td>
<td>(n = 51)</td>
</tr>
<tr>
<td>Hypokinesis inferior</td>
<td>14.5%</td>
<td>(n = 11)</td>
</tr>
<tr>
<td>Hypokinesis anterior</td>
<td>11.8%</td>
<td>(n = 9)</td>
</tr>
<tr>
<td>Hypokinesis septal</td>
<td>6.6%</td>
<td>(n = 5)</td>
</tr>
</tbody>
</table>

EF = ejection fraction

DISCUSSION

Among a patient population who underwent emergency coronary angiography for suspected acute coronary syndrome, significant coronary lesions could be documented in the majority of patients and most of them underwent catheter based revascularization. In a small group of patients, no angiographically detectable coronary artery disease was found. Echocardiography showed in 1/3 of patients in this group left ventricular segmental wall motion abnormalities and 21.1% had a reduced left ventricular systolic function. Particularly in patients with a conservative management of acute coronary syndromes, an individual risk stratification is of relevance. Patients with persistent wall motion ab-
normalities are at higher risk for adverse events [8].
Echocardiography is especially important for those pa-
tients that are not obviously at high risk. Patients with-
out clinical evidence of left ventricular dysfunction
may have significant wall motion abnormalities [8].
Our findings may be addressed by different aspects.

First, an acute coronary syndrome is followed by
myocardial ischemia with left ventricular segmental
wall motion abnormality but coronary angiography
does not detect a target lesion. Spontaneous peripheral
embolism of a ruptured coronary plaque may re-
establish coronary blood flow rapidly [13]. Furthermore,
early antithrombotic therapy that is initiated prior to
angiography may dissolve intraluminal thrombi which
therefore may not be seen by subsequent angiography
[14]. A relevant number of our patients without coro-
nary artery disease was treated with a multi-drug an-
tithrombotic regimen prior to angiography. Most of
them were on heparin, six patients underwent throm-
bolysis and in nine patients glycoprotein IIb/IIIa-in-
hibitors were administered. Thus, the fact of a normal
angiogram does not exclude a previous thrombotic
coronary event. This subgroup of patients has an in-
creased risk of ischemia related morbidity and mortal-
ty. Echocardiographically documented segmental wall
motion abnormalities in these patients stratifies this
particular subgroup at increased risk for adverse car-
diac events, although there is no clinical evidence of
left ventricular dysfunction. These patients may re-
quire a specific pharmacological treatment including
antiplatelets, CSE-blocker, beta-blocker or ACE-in-
hibitors although the angiogram did not reveal any ob-
vious coronary lesion.

Second, invasive findings of muscle bridges and
coronary spasms are strongly linked to occurrence of
myocardial ischemia [15, 16]. Myocardial bridges are
associated with an impaired endothelial function [17]
and may alter hemodynamic forces by the contraction
of the bridge itself [18]. Coronary spasms can cause
platelet aggregation and myocardial ischemia [19].
Therefore, documentation of wall motion abnormali-
ties in these cases may be expected.

In our study, 14.5% of patients had hypertensive
heart disease. Arterial hypertension and hypertensive
heart disease may contribute to myocardial ischemia
due to an increase in myocardial resistance and reduc-
tion of coronary flow reserve. Myocardial perfusion
abnormalities are frequently found with angiographi-
cally normal coronary arteries associated with left ven-
tricular hypertrophy or microvascular disease [20]. As
reported in a large study, in hypertensive patients, wall
motion abnormalities occurred in of 12.5% patients
and was associated with left ventricular hypertrophy
[21].

Moreover, in case of absence of myocardial is-
chemia, echocardiography may help to identify differ-
ent diagnoses. It can easily provide a non-invasive bi-
plane assessment of the left ventricle, heart valves and
pericardium. For example peri- or myocarditis may
cause dyscontractilities [22]. In patients with hyperten-
sive heart disease or cardiomyopathies, echo data pro-
vide major information for guiding long-term patient
management. A total of 27.5% of our patient popu-
lation were addressed as cardiomyopathy, pericarditis or
hypertensive heart disease representing a relevant
amount of patients in a group of suspected coronary
artery disease. Left ventricular function was decreased
severely in 5.3% of patients. These patients need fur-
ther assessment to evaluate their individual risk profile
and to identify patients requiring special treatment.

In summary, by detection of segmental wall motion
abnormalities in 1/3 of patients with suspected acute
coronary syndrome and normal angiogram, obviously,
ehocardiography is of clinical relevance. By identi-
fying patients at increased risk for adverse events or with
different diagnoses requiring further diagnostic evalua-
tion or treatment, clinical management of these pa-
tients includes echocardiographic findings. Recom-
mandations for performing echocardiography in pa-
tients with suspected acute coronary syndromes inde-
pendent of angiographic findings are strongly sup-
ported.

However, further studies are needed to evaluate the
impact of echocardiographic examinations in patients
with acute coronary syndromes and normal angiogra-
phy on clinical outcome and prognosis. These analyses
should implement echocardiographic techniques as
contrast and tissue doppler imaging [23, 24].

REFERENCES

College of Cardiology key data elements and definitions
for measuring the clinical measurements and outcomes of
patients with acute coronary syndrome. J Am Coll Cardiol
38:2114-2130
2. Bakshi TK, Choo MK, Edwards CC, Scott AG, Hart HH,
Armstrong GP (2002) Causes of elevated troponin I with
a normal coronary angiogram. Int Med J 32:520-525
Deyander S, Jager D, Machraoui A, Muegg A, Lemke B
(2005) Normal angiogram in acute coronary syndrome -
preangiographic risk stratification, angiographic findings
and follow-up. Int J Cardiol 99:19-23
A, McGuire DK, Wiens F, Sabatine MS, Morrow DA; de
Lemos JA (2006) Prevalence and determinants of tro-
ponin T elevation in the general population. Circulation
113:1958-1965
5. Burnett K, Feldman JA (2005) Noninvasive imaging tech-
niques to aid in the triage of patients with suspected acute
23:977-998
coronary syndromes. Heart 88:419-425
7. Lewis WR (2005) Echocardiography in the evaluation of
patients in chest pain units. Cardiol Clin 23:531-539
8. Romano S, Dagianti A, Penco M, Varveri A, Biffani E,
Fedele F, Dagianti A (2000) Usefulness of echocardiogra-
phy in the prognostic evaluation of non-Q-wave myocar-
dial infarction. Am J Cardiol 86:43G-45G
A, Fernandez-Aviles F, Fox KA, Hasdai D, Ohman EM,
Wallentin L, Wijns W (2007) Guidelines for the diagnosis
and treatment of non-ST-segment elevation acute coro-
nary syndromes. Eur Heart J 28:1598-1660
gement of acute myocardial infarction in patients pre-
senting with ST-segment elevation. Eur Heart J 24:28-66
Thrombolysis in myocardial infarction (TIMI) trial, phase
I: a comparison between intravenous tissue plasminogen
activator and intravenous streptokinase: clinical findings through hospital discharge. Circulation 76: 142-154


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