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ORIGINAL ARTICLE

Angiographic assessment of cardiac allograft vasculopathy: results of a Consensus Conference of the Task Force for Thoracic Organ Transplantation of the German Cardiac Society

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Summary

Angiograms of cardiac transplant (HTx) recipients were to be evaluated in a ring experiment and a joint consensus on criteria of angiographic evaluation of coronary arteries of HTx patients was to be reached. Twenty-four coronary angiograms from 11 hospitals were circulated. One hundred eighty-eight blinded evaluations were returned. A joint evaluation by six experienced cardiologists was used as reference standard and a consensus evaluation form was developed. Significant lesions (stenosis 75%, 50% in the left main coronary artery) were diagnosed in 10/23 abnormal coronary angiograms (41.7%). Interventional revascularization was recommended in 8/10 (80%). In 21 coronary angiograms distal pruning was found and in 11/21 (52.4%) cases with distal pruning occlusion of at least one peripheral vessel was detected. The best kappa value (0.7) was found for the presence of at least one clinically significant stenosis. Agreement on the site and grade of local stenosis was much less. Some agreement on remodeling was found in assessing diffuse narrowing in the LCA (kappa = 0.371, $P < 0.001$). The kappa value for peripheral obliteration was 0.331 ($P = 0.001$). Angiographic evaluation of cardiac allograft vasculopathy, particularly of diffuse and peripheral disease and remodeling, needs standardization. This should be performed in a downward compatible improvement process.

Introduction

Among heart transplant (Htx) recipients cardiac allograft vasculopathy (CAV) remains a major cause of long-term morbidity and mortality [1]. Criteria for angiographic diagnosis of CAV vary considerably. This results in limited validity and considerable variation of data on prevalence and incidence of CAV. In contrast to the common variety of coronary artery disease in nontransplanted hearts presenting with focal stenoses at predilection sites,

CAV is characterized by diffuse concentric intimal thickening in epicardial coronary arteries and also affects peripheral vessels [2–4]. Moreover, cardiac transplant recipients are not likely to develop angina pectoris, and the diffuse vascular involvement is associated with diffuse ischemia that eludes many noninvasive tests targeted at regional dysfunction. Thus routine surveillance angiography remains the standard diagnostic tool in clinical practice. A major shortcoming of this diagnostic approach is its moderate sensitivity for the detection of diffuse luminal narrowing [5]. Normal coronary angiograms were found in 8/10 patients dying from severe CAV [6]. Angiograms were normal in 62% of HTx patients with cardiac events [7]. The specificity of excluding CAV on the grounds of a 'normal' coronary angiogram was found to be only 81% [8]. There is a general agreement that intravascular ultrasound (IVUS) is the current method of choice to diagnose CAV in large epicardial vessels [9], but for reasons of costs and logistics its use is restricted to studies or similar clinical projects.

The goals of the study were

- to identify and measure inter-observer variability of angiographic signs of CAV,
- to provide tools to standardize the definition of CAV features with low repeatability,
- and to achieve and summarize a consensus on the evaluation of CAV.

Materials and methods

Goals and study design

Between 2007 and 2008, 11 German transplant centers each sent at least two anonymized films for assessment. The 24 films along with a preliminary evaluation form were circulated between the participating centers for blinded evaluation ('ring experiment'). The ring experiment was performed with anonymous retrospective data in accordance with the ethical standards laid down in the declaration of Helsinki and good clinical practice. A total of 188 blinded evaluations were returned from 8 centers between May 2008 and June 2009. The evaluation form was improved in usability in a downward compatible way and was used for joint reference evaluation by six experienced cardiologists from five centers at a consensus meeting held on June 12, 2009 in Münster, Germany. After thorough discussion, all participants agreed on a revised evaluation form for CAV, as well as on the diagnostic evaluation concerning the 24 coronary angiographies (reference standard).

Participating centers

Coronary angiographies were provided by Asklepios Hospital in Bad Tölz (2), Bad Krozingen (2), Hamm (2), Heidelberg (3), Ludwig Maximilian University (LMU) Munich (2 Grosshadern Hospital and 2 City Hospital), Erlangen (2), Hannover (2), Münster (5), and Deutsches Herzzentrum Berlin (2). Two centers, Marburg and Giessen, did not send coronary angiographies but joined the ring experiment and the consensus meeting.

Evaluation forms were returned from Berlin, Münster, Hannover, Bad Tölz, Munich LMU City Hospital, Marburg, Giessen, and Bad Oeynhausen.

Participants at the meeting in the University Hospital Münster were Dr. N. Hiemann, Dr. E. Wellnhofer, Dr. J. Stypmann, Dr. C. Bara, Dr. T. Stadlbauer, and Dr. M. Heidt.

Coronary angiograms and preliminary evaluation criteria

For evaluation and localization of stenosis the World Health Organisation/ International Society and Federation of Cardiology (WHO/ISFC) Task Force Scheme of 1986 was employed [10].

Additionally, specific morphologic features typical for CAV were evaluated based on a modified classification according to Gao [11] (see Fig. 1). The modifications are:

- Type A lesions are identified with focal stenosis, and are evaluated separately [10,12].
- Type B lesions (sub-types B1 and B2) are regarded as combinations of a diffuse remodeling defect of large (conduit) vessels combined with distal obliterations and/or pruning. Assessment is not lesion based, as in the original classification, but relates to the whole coronary artery. The result is documented as
  - **(i)** presence or absence of ectasia (type B1) or diffuse narrowing (type B2) in conduit vessels, and
  - **(ii)** occurrence of obliterations (thinning or pruning) or occlusions of peripheral vessels.
- Luminal irregularities in large vessels are documented as local diameter variations in conduit vessels with below 25% area reduction or abnormal tapering [13].

Revision of evaluation form

Assessment of macrovascular stenosis was revised based on current standards [10,12] with a focus on diagnostic or potential therapeutic consequences such as surveillance timing, percutaneous coronary intervention (PCI), or additional testing. For example, nonsignificant stenoses may trigger an IVUS examination or a shorter surveillance interval. A suspicious plaque may be further investigated by IVUS or optical coherence tomography [14] and/or sealed by PCI with stent [15,16]. Borderline stenosis might be handled by deferring PCI or assessing local ischemia invasively, for example by fractional flow reserve

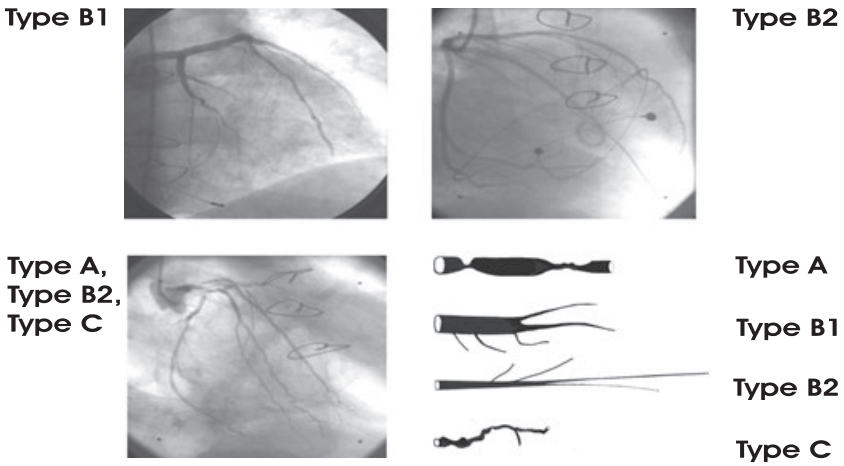

Figure 1 Gao classification.

[17,18]. Previous PCI without significant stenosis at the time of evaluation was considered.

The diagnostic complex of general vascular abnormalities was deemed important in CAV as an indicator of diffuse vessel wall abnormalities. The evaluation was subclassified into wall irregularities of large vessels, alterations in macrovascular remodeling in the left coronary artery (LCA) and right coronary artery (RCA), and peripheral obliterations (thinning/occlusion/pruning). The revised evaluation form is downward compatible with a modified Gao classification [11] because type B lesions are defined by distal obliteration along with different proximal remodeling patterns, whereas type A lesions are essentially stenotic disease. Type C lesions reflect severe diameter irregularities in the context of diffuse disease and do not seem to constitute a separate pathological entity [19].

The revised evaluation form (see Table 1) was approved by all participants of the consensus meeting*. Significant stenosis is defined as at least 75% area reduction in any coronary vessel or at least 50% area reduction in the left main coronary artery. A working definition of severe stenosis is given in terms of perfusion territory at risk and hazard. The finding of severe stenosis implies

a) either a significant stenosis of the proximal part of a major coronary artery (circumflex, left anterior descendent or right coronary artery) or the left main (perfusion territory at risk)

b) and/or a significant stenosis of at least two major branches or proximal or medial segments (multivessel disease, perfusion territory at risk)

c) and/or occlusion or stenosis exceeding 90% area reduction in a major branch or proximal or medial segment (hazard).

An additional item regarding vessels with increased tortuosity termed 'corkscrew' arteries is included. This morphology is regarded as indicative of hypertension [20]. This notion has been challenged recently, however [21]. The explosive mode of donor brain death was found to be the most significant determinant of hypertensive remodeling associated with increased graft vasculopathy and mortality [22]. Further issues were the diagnostic handling of patients without significant stenosis in the current angiogram but a history or evidence of previous PCI and of patients with stenotic lesions that are not severe by strict definition but look very hazy, suggesting thrombi or instable plaques. As plaque sealing is considered an emerging indication for PCI a specific item, 'borderline or suspicious plaque,' was introduced [15,16]. The finding of 'slow flow' that is regarded as indicative of the diffuse variety of atherosclerosis [23] was also introduced. Criteria for peripheral disease established at the meeting include the finding of occluded peripheral vessels and loss of taper at origin of small vessels. Regarding ectatic remodeling of large arteries the importance of giving a clearer definition was unanimously emphasized. A summary accounting for expected clinical implications was introduced. 'Normal' does not rule out minimal disease and implies deferral of angiographic follow-up. 'Mild' CAV suggests a tight surveillance schedule or further diagnostic or therapeutic intervention. This strategy takes into account the sensitivity bias of angiography and may imply the indication for an IVUS study. Grading as mild CAV may justify a change in immunosuppression or comedication and surveillance. 'Moderate' CAV implies an option for PCI and/or enhanced conservative treatment. 'Severe' CAV suggests acute or repeat PCI with drug-eluting stents or drug-eluting balloons and early invasive follow-up or even complete re-evaluation of therapeutic options including re-transplantation.

Statistics

Counts and percentages of findings are given. The blinded evaluations of the different centers were

compared with the reference standard by cross-table analysis. Sensitivity, specificity, and positive likelihood ratio were calculated. The positive likelihood ratio was preferred to positive predictive value in view of

Table 1. Revised evaluation form as table.

<table>
<tr><td>Quality</td><td>Poor</td><td>Moderate</td><td>Fine</td></tr>
<tr><td colspan="4"></td></tr>
<tr><td>Normal angiogram</td><td>No</td><td></td><td>Yes</td></tr>
<tr><td colspan="4">Stenosis, type A lesions</td></tr>
<tr><td>Any stenosis >25%</td><td>Yes</td><td></td><td>No</td></tr>
<tr><td>Significant stenosis</td><td>Yes</td><td>Borderline or suspicious plaque</td><td>No</td></tr>
<tr><td>Occlusion</td><td>Yes</td><td></td><td>No</td></tr>
<tr><td colspan="4">Stenosis % (S, coronary artery segment number)
<table>
<tr><th>S</th><th>≥50 <75</th><th>≥75 <99</th><th>≥99</th><th>S</th><th>≥50 <75</th><th>≥75 <99</th><th>≥99</th></tr>
<tr><td>1</td><td></td><td></td><td></td><td>9</td><td></td><td></td><td></td></tr>
<tr><td>2</td><td></td><td></td><td></td><td>10</td><td></td><td></td><td></td></tr>
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<tr><td>4</td><td></td><td></td><td></td><td>12</td><td></td><td></td><td></td></tr>
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<tr><td>7</td><td></td><td></td><td></td><td>15</td><td></td><td></td><td></td></tr>
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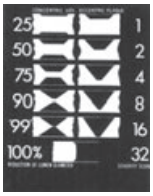

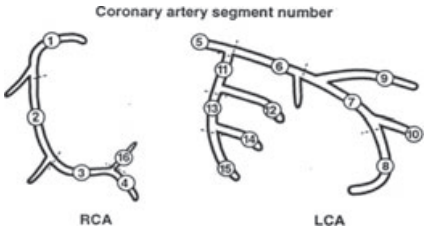
</td></tr>
<tr><td>Previous PCI/ stent</td><td>Yes</td><td></td><td>No</td></tr>
<tr><td>PCI indicated</td><td>Yes</td><td>Pending additional test</td><td>No</td></tr>
<tr><td colspan="4">Pending on:</td></tr>
<tr><td colspan="4">General features large vessels</td></tr>
<tr><td>RCA remodeling</td><td>Positive</td><td>Within normal range</td><td>Negative</td></tr>
<tr><td>LCA remodeling</td><td>Positive</td><td>Within normal range</td><td>Negative</td></tr>
<tr><td>Wall irregularities</td><td>Abnormal tapering</td><td>Diameter variations or 25% stenosis</td><td>Absent</td></tr>
<tr><td>Other</td><td>“corkscrew” arteries</td><td>Slow flow or pathologic TIMI grading</td><td>Absent</td></tr>
<tr><td colspan="4">Peripheral vessels</td></tr>
<tr><td>Normal and complete</td><td>No
<table>
<tr><td>Occlusions</td><td>Pruning</td></tr>
</table></td><td>Evaluation not possible</td><td>Yes</td></tr>
<tr><td colspan="4">Summary</td></tr>
<tr><td colspan="3">CAV
<table>
<tr><td>+ significant stenosis</td><td>+ peripheral vessel disease</td><td>+ history of PCI</td></tr>
<tr><td>Mild</td><td>Moderate</td><td>Severe</td></tr>
</table></td><td>Normal</td></tr>
</table>

unknown true prevalence. Agreement was assessed by kappa. The chi-square of the likelihood quotient was calculated and the variability of the evaluations was tested by the McNemar test.

Inter-observer variability between the centers was evaluated with the Friedman test. Significance was assumed at $P \leq 0.05$. We used the statistics package SPSS™ V.17 for evaluation.

Results

Inter-observer variability of angiographic signs of CAV

Eight centers returned a total of 154 evaluations of the 24 coronary angiograms (see Table 2).

The best agreement was found on the presence of at least one significant stenosis (kappa = 0.7, Friedman test not significant). The diagnosis of at least one significant stenosis was highly specific (specificity 94%) and moderately sensitive (sensitivity 75%) and demonstrated a positive likelihood ratio of 12.5. The agreement on site and grade of local stenosis was poor (kappa = 0.244, Friedman test $P < 0.001$). Fifty-seven percent (211/360) of segments with evidence of any stenosis, including 29% (106/360) of significant lesions, were missed by at least one of the observers. Only 26% (93/306) of blinded evaluations of stenosis agreed, with respect to severity and site, with the consensus evaluation. As expected in patients with predominantly diffuse disease the majority of findings (87% 2618/3008) were segments without stenosis. A stenosis >25% was excluded unanimously in 95% (2499/2618) in these segments. Luminal irregularities were a highly prevalent finding in the consensus evaluation. Agreement concerning luminal irregularities of the large vessels was poor (kappa = 0.108, Friedman test $P < 0.001$), because luminal irregularities were often described as multiple low-grade (10% or 25%) stenosis.

There were major issues regarding the remodeling characteristics of large conduit coronary arteries. The diagnosis of types B1 and B2 lesions did not agree between centers (Friedman test $P < 0.01$) probably due to the lack of clear criteria. The agreement on peripheral thinning or distal pruning of vessels was disappointing (kappa = 0.331, Friedman test $P < 0.001$).

Tools to standardize the definition of CAV features with low repeatability (see also Fig. 2)

The following suggestions may serve as working definitions.

In the case of multiple low-grade stenoses (e.g., area stenosis ≤25%) the description as diameter irregularities should be preferred.

Table 2. Inter-observer variability (Friedman test) and agreement (kappa, chi-square) and difference (McNemar test) between blinded evaluations with consensus assessment used as reference standard.

Parameter	Sensitivity	Specificity	Chi-square likelihood quotient	Positive likelihood ratio	Kappa	McNemar	Cross-table (*n*)	Friedman	Friedman /degrees of freedom (*n*)
Significant stenosis*	75% (60/80)	94% (101/108)	103	12.5	0.700	$P = 0.019$	188	$P = 0.363$	22/8
Stenosis evaluation†	—	—	513	—	0.244	$P < 0.001$	3008	$P < 0.001$	352/8
Luminal irregularities	65% (114/175)	63% (10/16)	4.6	1.8	0.108	$P < 0.001$	191	$P < 0.001$	21/7
Peripheral obliteration†	—	—	49.4	—	0.331	$P = 0.001$	177	$P < 0.001$	15/8
Ectasia LCA	6% (5/16)	76% (131/172)	0.4	0.3	0.040	$P < 0.001$	188	$P = 0.007$	22/8
Ectasia RCA	25% (10/40)	83% (123/148)	1.3	1.5	0.085	$P = 0.590$	188	$P = 0.004$	22/8
NR LCA‡	42% (30/72)	92% (107/116)	30.9	5.3	0.371	$P < 0.001$	188	$P < 0.001$	22/8
NR RCA‡	23% (9/40)	90% (133/148)	3.8	2.3	0.145	$P = 0.026$	188	$P < 0.001$	22/8

n, number of samples.
*≥75% or ≥50% in left main coronary artery.
†Three categories: normal peripheral vessels (severity grade 0), thinning, pruning (severity grade 1) or occlusion (severity grade 2).
‡NR: negative remodeling/diffuse narrowing.

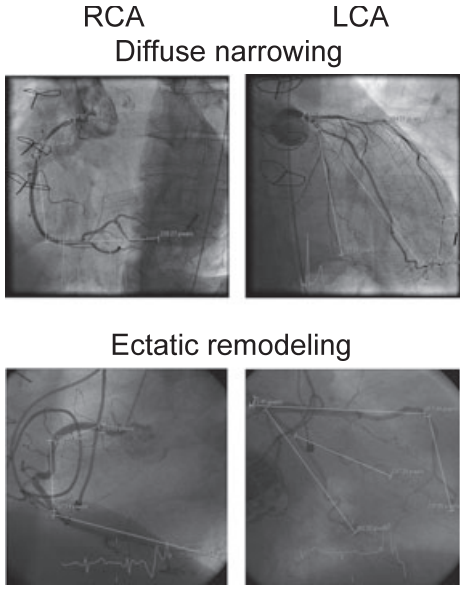

Figure 2 Assessment of conduit vessel remodeling. The estimated relation of ostial diameter to the length of the vessel is 0.01357 (7.07/521) in the diffusely narrowed RCA, 0.03037 (20.02/665) in the ectatic RCA, 0.01100 (13.6/1229) in the diffusely narrowed LCA and 0.01863 (23.41/1256) in the ectatic LCA. The pixel-based measurements were made with the Rubo DICOM Viewer™ on angiograms preclassified at the consensus meeting.

The definition of macrovascular remodeling in the angiogram is often based on a comparison of the lumen with catheter size. Physiological anatomic variances in the size of coronary arteries are large [24]. Therefore, this criterion is strongly influenced by the subjective judgement of the investigator. In cases of doubt it might be replaced by a parameter relating diameter and length of a coronary artery [25,26]. A simple approach to doing this with a digital imaging and communications in medicine (standard) (DICOM) viewer is illustrated in Fig. 2. Nondimensional numbers, such as the inlet diameter divided by the total length, are independent of the size of the heart [27]. The determination of length is hampered by foreshortening, however, and the accuracy of an estimation based on eyeballing is limited.

A more precise definition of the normal range for small diameter ratios of third- to second-order vessels may be derived from the measurements of Dodge *et al.* [24] in first- to second-order vessels in normal coronary arteries. These measurements suggest 0.3–0.5 as the rule of thumb for normal diameter ratios of third- to second-order vessels. Image quality is especially important in the evaluation of small vessels. Moreover, to avoid mixing up spastic and obliterated vessels, at least one angiographic scene after administration of nitroglycerin may be helpful.

Summary of consensus evaluation of coronary angiograms

Eight out of 24 angiograms were found to be of high and 16 of moderate quality. Coronary stenoses were found in 13/23 (56.5%) cases in the 23 coronary angiograms classified as abnormal. Twenty-nine significant lesions were diagnosed in 10/23 (41.7%) cases and 10 subtotal or complete occlusions were found in 6/23 (26.1%) patients. Revascularization of significant lesions including one subtotal occlusion was recommended in 8/23 (34.8%) patients. Intra-coronary stents were found in 8/23 (34.8%) coronary angiograms. Luminal irregularities of large conduit vessels were diagnosed in 22/23 (95.7%) and were deemed to be more severe in the majority, 18/23 (75%) of cases. Increased tortuosity of coronary vessels ('corkscrew' arteries) was found in 6/23 (25%) coronary angiograms.

Distal pruning of small vessels was found in 21/23 (91.3%) patients, and in 11/23 (47.8%) cases there was even evidence of peripheral occlusions. The overall severity of disease was rated on a scale from 0 to 4 (see Table 3). Significant stenosis or history of multiple PCI was found in 71%. Ectasia of large conduit vessels was diagnosed in only 2/23 (8.7%) left, but 5/23 (21.7%) right coronary arteries. Diffuse narrowing of conduit arteries was found in 9/23 (39.1%) left, but only 5/23 (21.7%) right coronary arteries.

Discussion

CAV is still a major cause of death in cardiac transplant recipients [1]. Therefore, epidemiologic data concerning its time-adjusted prevalence after transplantation are very important for the critical appraisal of current surveillance and therapeutic strategies. Existing data are not homogeneous and are biased with respect to varying diagnostic criteria and surveillance schemes. Specific diagnostic approaches target diffuse narrowing by assessing wall abnormalities and/or serial investigations and/or involvement of distal (tertiary) vessels by evaluating peripheral obliteration and pruning. The results are several paradigmatic definitions of angiographic CAV, as listed in Table 4:

- The significant stenosis approach [7,28–34].
- The stenosis approach with grading [35–37].
- The Gao classification variants [11,19,38,39].
- The any-disease-all-lesions variety [40–42].
- The combination of the (significant) stenosis approach
  - with distal pruning or obliteration [43–47]
  - with the Gao classification variants [48–53]
  - with TIMI-flow evaluation [54]

Table 3. Criteria for diagnostic grading of angiographic findings and prevalences found in the evaluated sample at the consensus meeting.

CAV	Grading	Criteria	*n*	%
None/normal	0	No or only minor abnormalities in angiogram	2	8
Mild	I	Definite macrovascular and/or peripheral abnormalities without previous PCI	1	4
Moderate	II	Significant stenosis and/or peripheral obstruction or previous PCI	4	17
Severe	III	Severe stenosis and/or peripheral occlusion or history of multiple PCI	17	71

PCI, percutaneous coronary intervention.
Significant stenosis: at least 75% area reduction or at least 50% area reduction in left main coronary artery.
Severe stenosis: (i) either significant stenosis of proximal part of major coronary artery (circumflex, left anterior descendent or right coronary artery) or left main (perfusion territory at risk), (ii) significant stenosis of at least two major branches or proximal or medial segments (multivessel disease), (iii) occlusion or stenosis exceeding 90% area reduction in a major branch or proximal or medial segment (reduced perfusion).

Table 4. Paradigmatic definitions of angiographic CAV and downward compatibility of revised evaluation approach.

Main feature	Additional feature	Special methods	Compatibility	Reference
Significant stenosis approach	Cut-off: 50–75%		Yes	[7,20–26]
Stenosis approach	+ grading		Yes	[27–29]
Gao classification variants			Yes	[11,30–32]
Any-disease-all-lesions variety			Yes	[33–35]
Stenosis (significant)	+ distal pruning or obliteration		Yes	[36–40]
	+ Gao classification variant		Yes	[41–46]
	+TIMI-flow evaluation		Partially	[47]
Serial diameter investigation		Quantitative coronary angiography (QCA)	No	[8,28,29,48].
Ischemic risk approach	+ residual ejection fraction	Stenosis weighted with respect to perfusion territory and ischemic cardiomyopathy	No	[49]
The 'Balk' grading system		Normal angiogram or only abnormal tertiary vessels, abnormal large vessels with wall irregularities or with focal lesions	Yes	[50]

- The serial diameter investigation [quantitative coronary angiography (QCA)] [8,36,37,55].
- The ischemic risk approach accounting for significant stenosis weighted with respect to perfusion territory and ischemic cardiomyopathy (residual ejection fraction) [56].
- The 'Balk' grading system: normal angiogram or only abnormal tertiary vessels, abnormal large vessels with wall irregularities or with focal lesions [57].

The Working Group on Thoracic Organ Transplantation of the German Cardiac Society decided to tackle this problem because the bulk of data on CAV stems from 'insensitive' angiography. First, critical issues in inter-observer variability should be identified. In a second step definition of criteria for angiographic evaluation should be improved. The quality assurance approach in clinical laboratories by regular blinded evaluation of test samples ('ring experiment') was adopted for this purpose.

A collection of features of angiographic CAV was evaluated to identify and measure inter-observer variability.

The kappa values concerning significant stenosis in epicardial vessels (Table 2) agreed with published data (kappa = 0.72), as opposed to assessment of peripheral obliteration [57]. This is probably due to the fact that only two centers took part in the study cited [57] whereas in our study a larger variety of centers participated, resulting in an increased spread of schools of diagnostic approach to angiographic evaluation. Peripheral vessels are not a focus of conventional oculostenotic angiographic assessment and their assessment lacks standardization. There is only limited data on inter-observer variability in angiographic evaluation of CAV. In patients without heart transplantation the reproducibility data from the Coronary Artery Surgery Study (CASS) study apply for the assessment of significant stenosis [58].

Improved definitions are needed, as is strongly supported by the rather poor agreement between different blinded investigators on diffuse vessel wall abnormalities.

Macrovascular remodeling in CAV has a specific time course and does not depend on atheroma burden alone [59–63]. As changes in geometry have an impact on wall shear stress, which influences remodeling, evaluation of macrovascular luminal geometry is expected to provide additional prognostic information [64,65]. Sluggish flow in ectatic coronary arteries may be quantified by TIMI frame count and used as an indirect criterion [54]. Performing a classification is not compelling, but the item is meant as a reminder to look at remodeling.

In ambiguous cases and in poor quality angiograms an assessment of small vessels may not be feasible. The clinical importance of having a look at small vessels derives from the independent risk due to microvasculopathy in CAV [66]. The clinical impact may be a switch in medical treatment and/or an evaluation by biopsy.

The usability of the 'complicated' system of reporting was evaluated in Münster. An experienced angiographer may do the assessment within 15 min. A large part of this time is spent in waiting for the loading of DICOM runs into memory. The form was designed to provide a hierarchical framework of optional clinically relevant items, which are compatible to and meant to improve existent commonly used varieties of angiographic evaluation. The form is a prototype embedded into the philosophy of continuous improvement. Further evaluation is underway.

Limitations

A major limitation of the study is the limited number of participating centers and the small number of angiograms. This is aggravated by the fact that not all participants provided an angiogram or returned an evaluation. The resulting uncertainty is confined to the objective of assessment of inter-observer variability and is reflected by a large variance, which is enhanced by evolving changes between the initial and revised evaluation form and inclusion of outliers. Angiography is not a very sensitive diagnostic approach for CAV [5,6,8], but more sensitive techniques such as IVUS lack widespread comprehensive clinical use and are not indicated to assess peripheral coronary vessels. Thus, IVUS is not the preferred method to assess the prevalence of CAV, because sampling of CAV by IVUS studies depends on the true prevalence of the disease and may depend on the policies of IVUS performance at a particular center. Routine evaluation of angiograms relies on soft criteria and depends on angiographic quality and the observer [58]. Evidence relating coronary morphology in CAV with prognosis is limited. We do not know whether more severe lesions in large conduit vessels portend a worse prognosis than distal pruning or enlargement remodeling with sluggish flow. The ring experiment, and in particular the consensus evaluation, was therefore an important approach to evaluate and improve the agreement in angiographic evaluation of CAV. It also revealed critical points, where clearer definitions need to be developed, for example, macrovascular remodeling.

Conclusion

In terms of continuous quality improvement, standardized evaluation of coronary angiograms in cardiac transplant recipients will be a necessary continuous learning process. On the other hand, consistency and comparability of diagnostic evaluations must be assured. Thus, in analogy to software updates, compatibility of diagnostic evaluations is a major issue. This compatibility approach allows some improvement by retaining comparability. A major challenge is to mine implicit subconscious expertise of evaluators and to cast it into clear, explicit, usable definitions or rules. This may be facilitated by comparing different modeling approaches and statistical analysis. A repeat ring experiment including a consensus evaluation possibly based on a wider European or international ring of participants would be a further step to reduce inter-observer variance and to standardize assessment of CAV features with low repeatability.

Authorship

EW wrote the paper. NEH designed and managed the study. All authors took part in the design of the study and in the discussion of the paper. TS and MCH did not send coronary angiographies, but joined the ring experiment and the consensus meeting. Evaluation forms were returned from Berlin, Münster, Hannover, Bad Tölz, Munich LMU City Hospital, Marburg and Giessen, Bad Oeynhausen.

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