Europace (2012) **14**, 1639–1645
doi:10.1093/europace/eus161

High-degree atrioventricular block complicating ST-segment elevation myocardial infarction in the era of primary percutaneous coronary intervention

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Received 9 March 2012; accepted after revision 18 April 2012; online publish-ahead-of-print 29 May 2012

Aims Primary percutaneous coronary intervention (pPCI) has replaced thrombolysis as treatment-of-choice for ST-segment elevation myocardial infarction (STEMI). However, the incidence and prognostic significance of high-degree atrioventricular block (HAVB) in STEMI patients in the pPCI era has been only sparsely investigated. The objective of this study was to assess the incidence, predictors and prognostic significance of HAVB in STEMI patients treated with pPCI.

Methods and results This study included 2073 STEMI patients treated with pPCI. The patients were identified through a hospital register and the Danish National Patient Register. Both registers were also used to establish the diagnosis of HAVB. All-cause mortality was the primary endpoint. During a median follow-up of 2.9 years [interquartile range (IQR) 1.8–4.0] 266 patients died. High-degree atrioventricular block was documented in 67 (3.2%) patients of whom 25 died. Significant independent predictors of HAVB included right coronary artery occlusion, age >65 years, female gender, hypertension, and diabetes. The adjusted mortality rate was significantly increased in patients with HAVB compared to patients without HAVB [hazard ratio = 3.14 (95% confidence interval 2.04–4.84), $P < 0.001$]. A landmark-analysis 30 days post-STEMI showed equal mortality rates in the two groups.

Conclusion The incidence of HAVB in STEMI patients treated with pPCI has been reduced compared with reports from the thrombolytic era. However, despite this improvement high-degree AV block remains a severe prognostic marker in the pPCI era. The mortality rate was only increased within the first 30 days. High-degree atrioventricular block patients who survived beyond this time-point thus had a prognosis equal to patients without HAVB.

Keywords Atrioventricular block • Myocardial infarction • Primary percutaneous intervention

Introduction

High-degree atrioventricular block (HAVB) complicating acute myocardial infarction (AMI) is known to be an ominous prognostic marker associated with an increased rate of mortality.[1–8] The overall incidence of HAVB in AMI patients is reported to be 2–13% depending on the type and anatomical location of the AMIs investigated.[1–6,9,10] Patients with inferior AMI are considerably more prone to HAVB development and have a two- to four-fold increased risk of HAVB compared with patients with anterior location of the AMI.[2,5,10] ST-segment elevation myocardial infarction (STEMI) also increases the risk of HAVB compared with patients with non-STEMI.[6,9,10] Improved therapeutic interventions for both the acute- and later phases of AMI have caused the

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What's new?

- The incidence of high-degree atrioventricular block (HAVB) complicating ST-segment elevation myocardial infarction (STEMI) has decreased as the implementation of primary percutaneous coronary intervention (pPCI) as guideline-recommended treatment-of-choice.
- The markedly adverse prognostic significance of HAVB after STEMI, even when treated by appropriate pPCI, has not decreased compared with accounts from the thrombolytic era.
- Several clinical patient characteristics are predictive of HAVB development in STEMI patients treated with pPCI. These include right coronary artery (RCA) occlusion, age >65 years, female gender, hypertension, and diabetes.

incidence of HAVB in this setting to decline over the last few decades.[6,9] Several clinical and demographic patient characteristics have been identified as predictors of HAVB development in AMI patients including older age, female sex, inferior AMI, prior AMI, smoking, hypertension, and diabetes.[1,5,11]

Prior studies have demonstrated the severe clinical repercussions of HAVB in AMI patients both before[10–19] and after[1–9] the onset of the thrombolytic era. A few studies have included patients undergoing primary percutaneous coronary intervention (pPCI) but no studies have exclusively focused on the implications of HAVB in patients undergoing guideline recommended pPCI for acute STEMI.[4,6,8,20] As most STEMI-patients are currently treated by pPCI, it is highly relevant to clarify whether this therapeutic approach has changed the rate and prognostic significance of HAVB development following a STEMI.

The purpose of this study was to describe the characteristics of patients who develop HAVB, and assess the incidence and prognostic significance of HAVB in a large cohort of consecutive STEMI patients treated with pPCI.

Methods

Patients and study design

The study included 2073 Danish citizens admitted to our tertiary cardiac centre at Gentofte University Hospital in Denmark with STEMI for pPCI over a 4-year period. The included patients were identified through a dedicated hospital register of patients admitted for acute coronary syndrome. Patients were, in accordance with national recommendations, hospitalized for a minimum of 5 days following the STEMI. As patients could be transferred to other hospitals during the course of their admission, the Danish National Patients Register was used to track the entire course of admission.

Baseline demographic and clinical data

Baseline demographic and clinical data were collected prospectively from all patients on admission and entered in the dedicated hospital register. Hypertension, diabetes, and congestive heart failure were defined by the use of drugs targeting these diseases. Multivessel disease was defined as two or more than two major epicardial coronary arteries with >50% stenosis. Type C-lesions were considered complex lesions. Recurrent AMI was defined as reappearance of chest pain combined with a significant increase in cardiac biomarkers >5 days after the pPCI.

Peak values of cardiac biomarkers were retrieved from a regional database. In the study follow-up period the guidelines and assays for measurement of cardiac biomarkers in acute coronary syndrome changed more than once. Troponin-I, troponin-T, creatine kinase MB, and combinations of the three were used. Thus, the information on the included patients was heterogeneous and no single biomarker was available during the entire study period.

Left ventricular ejection fraction (LVEF) estimated by transthoracic echocardiography (TTE) was found in the departments' database of echocardiographic studies. Left ventricular ejection fraction is routinely estimated by TTE after STEMI. If indicated by the clinical circumstances (hemodynamically unstable patients) it is performed immediately. Consequently, LVEF estimates in patients belonging to the Gentofte University hospitals' uptake area, patients who had indications for acute examination and patients belonging to other hospitals who could not be transferred before day 5 post-PCI procedure were available.

ST-segment elevation myocardial infarction and primary percutaneous coronary intervention

ST-segment elevation myocardial infarction was defined as the presence of chest pain for >30 min associated with a cumulative persistent ST-segment elevation >4 mm in at least two contiguous precordial electrocardiogram (ECG)-leads or >2 mm in at least two or more contiguous limb ECG-leads or new-onset left bundle branch block.

Primary PCI was performed according to contemporary interventional guidelines.[21]

High-degree atrioventricular block

To establish the diagnosis of HAVB during the admission, we searched the aforementioned hospital register and the Danish National Patient Register for ICD-10 codes of AV block, bradycardia, and procedure codes of implantation of temporary transvenous paceelectrode and Zoll pacing.

High-degree atrioventricular block was defined as second- and third-degree AV block. Medical records were retrieved from the hospital archives and individually evaluated in all patients with a matching diagnosis or procedure code in the registries. The patients only received a final diagnosis of HAVB if ECG documentation was available, if the pPCI-operators' procedural description contained the diagnosis or if the attending ward physicians clinical chart statements directly confirmed the diagnosis.

Endpoints

All-cause mortality was used as primary endpoint. The vital status of all included patients was obtained from the Danish National Person Identification Register. The Danish National Register of Cause of Death was used to identify the diagnosis codes of the individual events of death. Subsequently, deaths were classified as cardiac, non-cardiac, or unknown. Cardiac death was examined as a secondary endpoint.

Statistics

All demographic and clinical characteristics at baseline were compared for patients with and without HAVB using χ^2 test or Fisher's exact test.

A multivariate logistic regression model was fitted to evaluate the association between baseline demographic and clinical characteristics and HAVB.

The cumulative probability of the primary endpoint in patients with and without HAVB was estimated by the Kaplan–Meier method and significance testing was performed by a log-rank test. The survival function estimates were plotted to illustrate the time to death. A similar approach was used to conduct a landmark analysis at day 30 after STEMI.

To test whether second- and third-degree AV block had the same prognostic effects, we conducted a subgroup analysis. Time to HAVB was plotted against the probability of mortality.

Univariate Cox proportional hazards regression analysis was used to estimate the risk of death associated with HAVB. A multivariate Cox analysis was fitted including all baseline demographic and clinical characteristics. Recurrent AMI was additionally included as a time-dependent covariate. An identical model was utilized to estimate the risk of the secondary endpoint cardiac death.

Subgroup analyses, regarding the prognostic influence and overall model modulations of post-STEMI peak level of cardiac biomarkers and LVEF, were also performed by Cox proportional hazards regression analyses including all patients with available measurements. A model was constructed for each of the individual biomarkers and LVEF. The models included the same covariates as in the overall multivariate model outlined above.

All analyses were done using SAS 9.1.3 (SAS Institute, Cary, NC, USA). Two-sided *P* values of <0.05 were considered statistically significant.

Table 1 Baseline characteristics of the 2073 patients

	HAVB ($n = 67$)	No HAVB ($n = 2006$)	*P* value
Demographic characteristics (%)			
Age >65 years	69	42	<0.001
Male gender	51	73	<0.001
Current smoker	54	52	0.829
Medical history (%)			
Diabetes	19	10	0.008
Treatment for hypertension	54	33	<0.001
Congestive heart failure	9	4	0.033
Prior AMI	7	8	0.948
Clinical findings at admission (%)			
Systolic BP < 90 mmHg	6	3	0.115
Findings at coronary angiography (%)			
Culprit lesion vessel			<0.001
Left main coronary artery	2	1	
Circumflex artery	4	9	
Left anterior descending artery	13	46	
Right coronary artery	79	37	
Other	2	7	
Complexity level of culprit lesion*			0.148
A	6	10	
B	40	43	
C	54	47	
Multivessel disease	42	33	0.264

Baseline characteristics were compared using χ^2 test or Fisher's exact test.
**P* value corresponds to comparison of type C lesions vs. other lesions.

Ethics

Appropriate approvals were obtained from the local ethics committee, the Danish National Board of Health and the Danish Data Protection Agency. The authors had full access to the data and assume responsibility for its integrity. The study complies with the declaration of Helsinki and all supplements hereof.

Results

High-degree atrioventricular block

Of the 2073 patients, 67 (3.2%) had HAVB during the course of hospitalization. Fifty-six of the events were third-degree AV blocks. Of the 11 second-degree AV block events one was Mobitz type I, two were of Mobitz type II, five were advanced blocks, and three were unspecified. The vast majority (91%) of the HAVB events occurred within 48 h. In patients with RCA culprit lesions ($n = 804$), the HAVB incidence was 7% ($n = 53$) whereas the incidence was 1% ($n = 9$) in left anterior descending artery (LAD) infarctions ($n = 928$). Of the remaining five HAVB events, three occurred after infarctions in the left circumflex artery, one in left main coronary artery and one in another vessel.

Baseline characteristics are displayed in *Table 1*. High-degree atrioventricular block was more common in patients who were older and female. Diabetes, hypertension, and congestive heart failure were also significantly more frequent in HAVB patients. Right coronary artery was more often the location of the culprit lesion in the HAVB patients. Right coronary artery culprit lesion, age >65 years, female gender, hypertension, and diabetes were found to be independent predictors of HAVB (*Table 2*).

Of the 67 patients who developed HAVB, 53 had a temporary pacing system implanted subsequent to the event. Three patients experienced cardiac tamponade following the temporary lead placement. One event was lethal, one required surgical evacuation, and the last one was treated conservatively.

Table 2 Independent predictors of high-degree atrioventricular block

Parameter	Odds ratio	95% CI	*P* value
RCA culprit lesion	5.95	3.25–10.90	<0.001
Age >65 years	2.45	1.39–4.52	0.002
Female gender	1.92	1.15–3.22	0.013
Treatment for hypertension	1.77	1.05–2.98	0.032
Diabetes	2.15	1.10–4.18	0.024

The logistic regression model included the following non-significant parameters besides the above tabulated; congestive heart failure, smoking status, type C complexity of culprit lesion, prior acute myocardial infarction, multi-vessel disease and systolic blood pressure < 90 mmHg at admission.

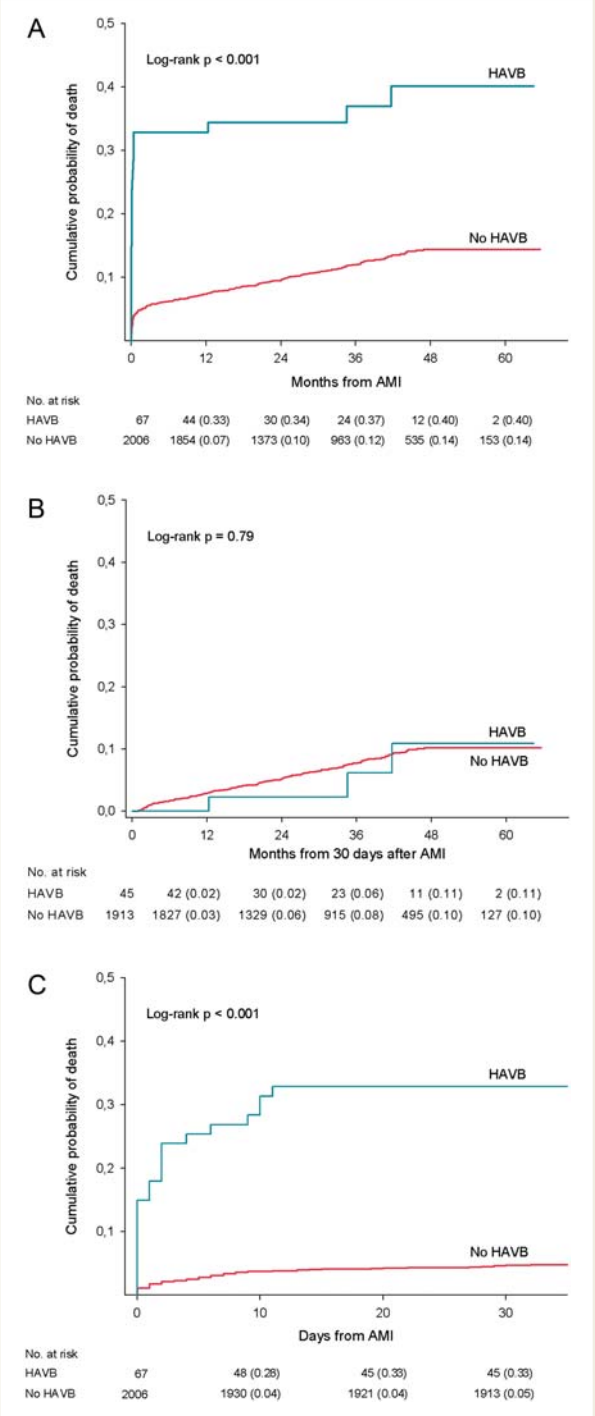

Figure 1 Survival curves of patients with and without high-degree atrioventricular block complicating ST-segment elevation myocardial infarction. Kaplan–Meier plot of the cumulative probability of death stratified by high-degree atrioventricular block (A). Landmark analysis corresponding to 30 days after acute myocardial infarction (B). Kaplan–Meier plot of the cumulative probability of death within the first 30 days after acute myocardial infarction stratified by high-degree atrioventricular block (C).

Mortality

In total, 266 patients died during the median follow-up of 2.9 years [interquartile range (IQR) 1.8–4.0]. Death was classified as cardiac in 144 patients, non-cardiac in 103 patients, and unknown in 19 patients. Of the patients who died from cardiac causes, 19 had HAVB.

Of the 67 patients diagnosed with HAVB, 25 patients eventually died. The median time to death in the HAVB patients was 1.5 days (IQR 0–9) whereas it was 132 days (IQR 6–641) in the patients without HAVB.

Of the 98 patients with RCA infarctions who died, 19 (20%) had HAVB. Among the 131 patients with LAD lesions who died, 5 (4%) had HAVB.

Figure 1 illustrates the survival probability of patients with and without HAVB. The mortality rate was significantly higher in the HAVB patients (panel A). The landmark analysis of survival in patients alive at day 30 post-STEMI shows that the rate of mortality was similar in the two groups (panel B). Within the first 30 days after STEMI the probability of death was 33% in the HAVB group vs. 5% in the non-HAVB patients (panel C). Patients with third-degree AV block had a significantly reduced estimated survival similar to the overall HAVB group (44 vs. 14%, log-rank $P < 0.001$) while patients with second-degree AV block did not (27 vs. 15%, log-rank $P = 0.14$).

In the univariate Cox regression analysis, the hazard ratio of death was found to be 4.06 [95% confidence interval (CI) 2.69–6.14] in patients with HAVB compared to patients without HAVB. The results of the multivariate Cox regression analysis are shown in *Figure 2*. The model included all the listed covariates of which HAVB, age >65 years, and prior medical treatment for hypertension or heart failure were significantly more frequent in the patients who died. High-degree atrioventricular block was in the multivariate model found to be an independent predictor of death with a hazard ratio of 3.14 (95% CI 2.04–4.84). With regard to the secondary endpoint cardiac death, HAVB also proved an independent prognostic marker with a hazard ratio of 4.96 (95% CI 2.95–8.32).

The subanalyses on the subgroups of patients with measurements of cardiac biomarkers and LVEF are shown in *Table 3*. Troponin-I and LVEF were both found to be prognostic of overall mortality. High-degree atrioventricular block remained an independent predictor of death in all four subanalyses. The risk estimate of HAVB on mortality was in all four analyses similar to the overall multivariate model.

Discussion

This study is, to our knowledge, the first to assess the incidence and prognostic significance of HAVB complicating STEMI in the pPCI era. In this large cohort of consecutive STEMI patients treated at a high-volume PCI-centre, we found a relative reduction of 40–60% in the overall incidence of HAVB complicating STEMI compared with reports from the thrombolytic era. Particularly, the occurrence of HAVB beyond the first two days after pPCI-treated STEMI was reduced by up to 10% in absolute numbers. However, despite this improvement HAVB remains a severe

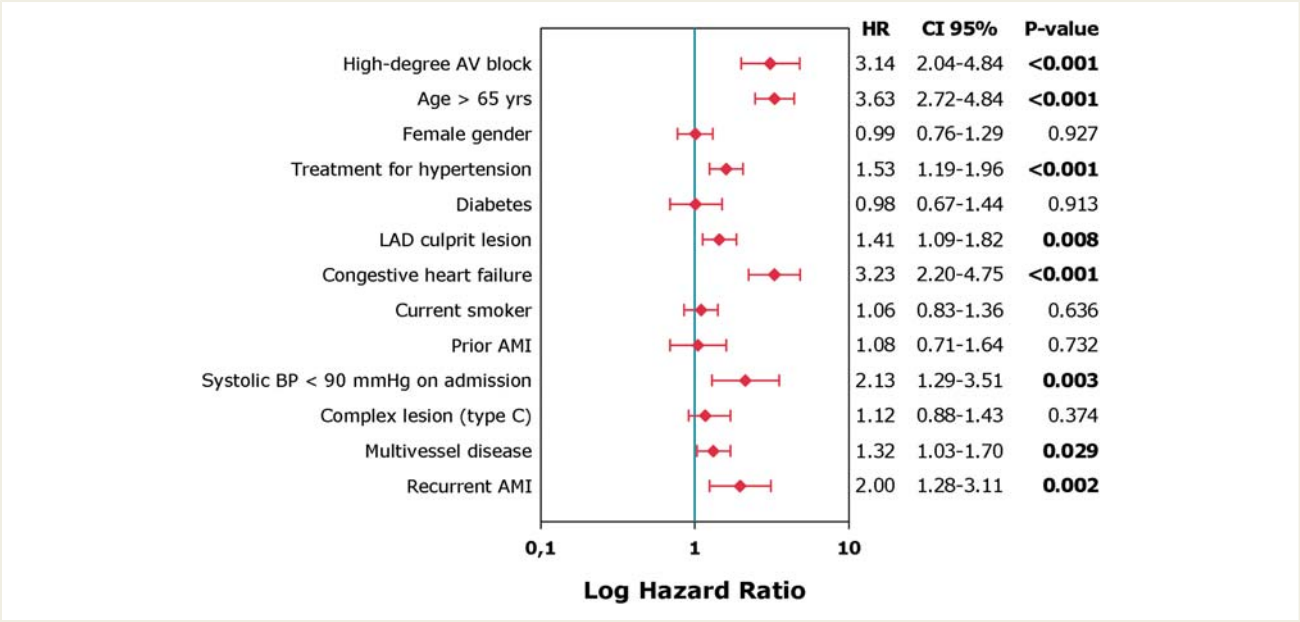

Figure 2 Prognostic value of high-degree atrioventricular block and clinical patient characteristics. The fitted multivariate Cox regression model included all baseline demographic and clinical data. Additionally, recurrent acute myocardial infarction was added to the model. Prior acute myocardial infarction was defined as acute myocardial infarction prior to the index admission. Recurrent acute myocardial infarction was defined as acute myocardial infarction occurring minute. Five days subsequent to the index admission.

Table 3 Cardiac biomarkers and left ventricular ejection fraction

Parameter	*N*	Median (interquartile range)	Hazard ratio	95% CI	*P* value
Troponin-I (μg/L)	1356	111 (33–249)	1.007	1.001–1.014	0.032
HAVB			2.507	1.349–4.658	0.004
Troponin-T (μg/L)	1123	4 (2–8)	1.022	0.993–1.051	0.133
HAVB			2.477	1.398–4.388	0.002
Creatine kinase MB (μg/L)	1888	206 (74–406)	1.004	1.000–1.008	0.056
HAVB			3.148	1.998–4.959	<0.001
LVEF (%)	610	40 (30–50)	0.790	0.701–0.890	<0.001
HAVB			3.076	1.014–9.331	0.047

The table displays the results of the four separate multivariate Cox regression subanalyses performed on subgroups of patients with available values of the individual cardiac biomarkers and LVEF. Each double-row (separated by solid lines) represents a single analysis. The utilized models were identical to the overall multivariate model except that in each one a cardiac biomarker or LVEF was added. The number of patients included in the analyses and the median of the measurements are shown in the first two columns. Only the risk estimates of the cardiac biomarkers, LVEF and HAVB in the individual analyses are displayed. Hazard ratios are given for an increase of 1 μg/L in troponin-T and 10 μg/L creatine kinase MB, and troponin-I. Hazard ratio for LVEF is given for a decrease of 5%.

prognostic marker in the pPCI era. Patients presenting with HAVB during the hospitalization following STEMI thus continue to have a significantly increased rate of mortality. High-degree atrioventricular block patients were more than three times as likely to die within the follow-up period compared with patients without HAVB.

Incidence

The incidence of HAVB in this study was found to be 3.2% overall which is 2–4% lower than reported in studies of STEMI patients in the thrombolytic era.[2,5] Both Nguyen *et al.*[6] and Harpaz *et al.*[1] found incidence rates similar to or even lower than ours. However, these studies included non-STEMI patients who are not at the same risk of HAVB.

Only 9% of HAVB events occurred after 48 h in our study. Reports from the thrombolytic era demonstrated incidence rates of up to 20%.[2] This indicates that pPCI as treatment-of-choice for STEMI might attenuate the risk of late occurring HAVB.

Aplin *et al.*[2] reported a HAVB incidence of 9.4% in patients with inferior infarctions and 2.5% in anterior infarctions which is slightly higher than our findings of 7 and 1% in patients with RCA and LAD culprit lesions, respectively.

Besides RCA as culprit lesion, our study identified age >65 years, female sex, treatment for hypertension, and diabetes as independent predictive markers of HAVB development. This is in accordance with previous investigations.[5]

Our results indicate that the vast majority of the HAVB events after STEMI treated by pPCI are transient. Only six (9%) patients required implantation of a permanent pacemaker prior to discharge as a consequence of persistent or recurring HAVB. This aligns with the results of previous studies and corresponds well with the theories of pathophysiology of HAVB in the setting of a recent STEMI.[22–25]

We found a 6% risk of cardiac tamponade as a complication to acute temporary pacing lead placement. This emphasizes the necessity of careful consideration when determining emergency pacing modality.

Aetiology

The aetiology of HAVB in the setting of STEMI is thought to be multifactorial and dependent on the location of the culprit lesion. The AV nodal artery normally arises from the distal RCA.[26] Collateral arterial blood supply to the AV node is provided by septal branches of the proximal LAD. High-degree atrioventricular block is usually located above the His bundle if complicating STEMI with occlusion of RCA while it is usually infra-Hissian in LAD lesions. The conduction tissue of the AV node is resistant to permanent damage from ischaemia due to the high intracellular contents of glycogen, the rich, complex arterial blood supply and the capability of nutrient and oxygen absorption by diffusion from surrounding venous sinusoids.[23] However, the ischaemic insult of a STEMI is thought to be sufficient to cause a transient dysfunction of the conduction fibres. Only in a minority of cases, typically LAD culprit lesions with extensive myocardial damage, is the HAVB therefore caused by infarction and necrosis of the conductive tissue. Otherwise, HAVB is thought to be provoked by enhanced parasympathetic tone or local release of potassium or adenosine or a mixture of all the mentioned mechanisms.[27] These mechanistic considerations contribute to the understanding of the transiency of the majority of HAVB events, which was also evident in our study.

In the thrombolytic era, it was shown that thrombolytic therapy precipitated the development of HAVB.[1,8] The effect is suspected to originate from the revascularization inducing a surge of afferent vagal activity that in turn induces a transient HAVB. Whether this effect is different when reperfusion is achieved by intracoronary stenting is unknown.

Mortality

High-degree atrioventricular block was associated with a significantly increased risk of both overall mortality and cardiac death, independently of all other clinically important confounders under study. High-degree atrioventricular block has consistently been found to mark an adverse short-term mortality whereas the long-term impact is questionable.[1–3,5,11] This is in accordance with our findings. A pronounced difference in the probability of survival was evident even after 5 years, between patients with and without HAVB. However, the rate of mortality was similar in the two groups already after 30 days and the landmark analysis of 30-day survivors showed no difference in outcome. Thus, after 30 days HAVB patients had the same risk of death as demonstrated in non-HAVB post-STEMI patients.

The observed differences in mortality of HAVB patients with RCA and LAD culprit lesions of the STEMI most likely reflect a difference in the underlying pathophysiology as discussed above. Approximately 55% of patients with HAVB complicating LAD occlusion died compared with only 36% of patients with RCA occlusion. This is most likely explained by more extensive infarctions when LAD is culprit lesion.

The subanalyses on cardiac biomarkers, as surrogate measures of infarction size, revealed that HAVB remained associated with an increased risk of mortality. Similarly, the estimate of prognostic impact of HAVB was significant and virtually unchanged in the subanalysis on post-STEMI left ventricular function assessed as LVEF by TTE.

Clinical implications

Three important clinical implications must be emphasized from our study. Firstly, our results support the use of pPCI as treatment-of-choice for STEMI patients as we observed a remarkable reduction in the incidence of HAVB using this treatment. Secondly, patients with HAVB complicating STEMI require special attention in the course of admission as the prognostic impact of HAVB has unfortunately not been reduced compared with the thrombolytic era. Thirdly, it seems that 30 days post-STEMI the mortality rates of HAVB and non-HAVB patients are equal indicating that if managed appropriately these patient have the same prognosis.

Study limitations

Ideally, the estimate of reduction in incidence of HAVB after STEMI in the era of pPCI should include a control group consisting of STEMI patients treated with thrombolysis in the same time period at our invasive centre. However, as the strategy of reperfusion was uniform in the study period, namely pPCI, such a study is not possible. Our study is therefore limited to a comparison to historical cohorts.

Our study had incomplete data on LVEF and peak values of cardiac biomarkers. These are widely acknowledged as important risk markers of mortality after STEMI. The conducted subanalyses regarding these factors consistently showed that HAVB was an independent significant prognostic marker despite adjustment for these factors. Information on all included patients on these variables could possibly have modified our estimate of the impact of HAVB after STEMI. However, the multivariate Cox analysis was adjusted for an extensive number of covariates adversely predictive of patient outcome after STEMI and in spite of this HAVB remained an independent ominous prognostic marker.

All registers have an innate risk of underreporting which in our study could lead to underestimation of the HAVB incidence. The Danish registers are, however, unique in their validity and HAVB is a significant clinical event unlikely to be omitted. Thus, we believe this to be of only minor influence.

Conclusion

In 2073 consecutive STEMI patients treated with pPCI, we found HAVB to be independently predicted by age >65 years, female sex, RCA occlusions, diabetes, and hypertension. The incidence of HAVB complicating STEMI has been reduced in the pPCI era compared with the thrombolytic era. However, the short-term adverse prognosis associated with HAVB remains unaffected. Beyond 30 days post-STEMI the prognosis is equal regardless of whether the patient had HAVB in the acute phase.

Acknowledgements

We are indebted to all the PCI operators and treating physicians at the Department of Cardiology at Copenhagen University Hospital Gentofte.

Conflict of interest: P.E.B.T. has received research grants and speakers fees from Boston Scientific, St Jude Medical, and Medtronic Inc. No other authors declare possible conflict of interest.

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