Cardiac imaging characteristics of patients with COPD: prognostic implications

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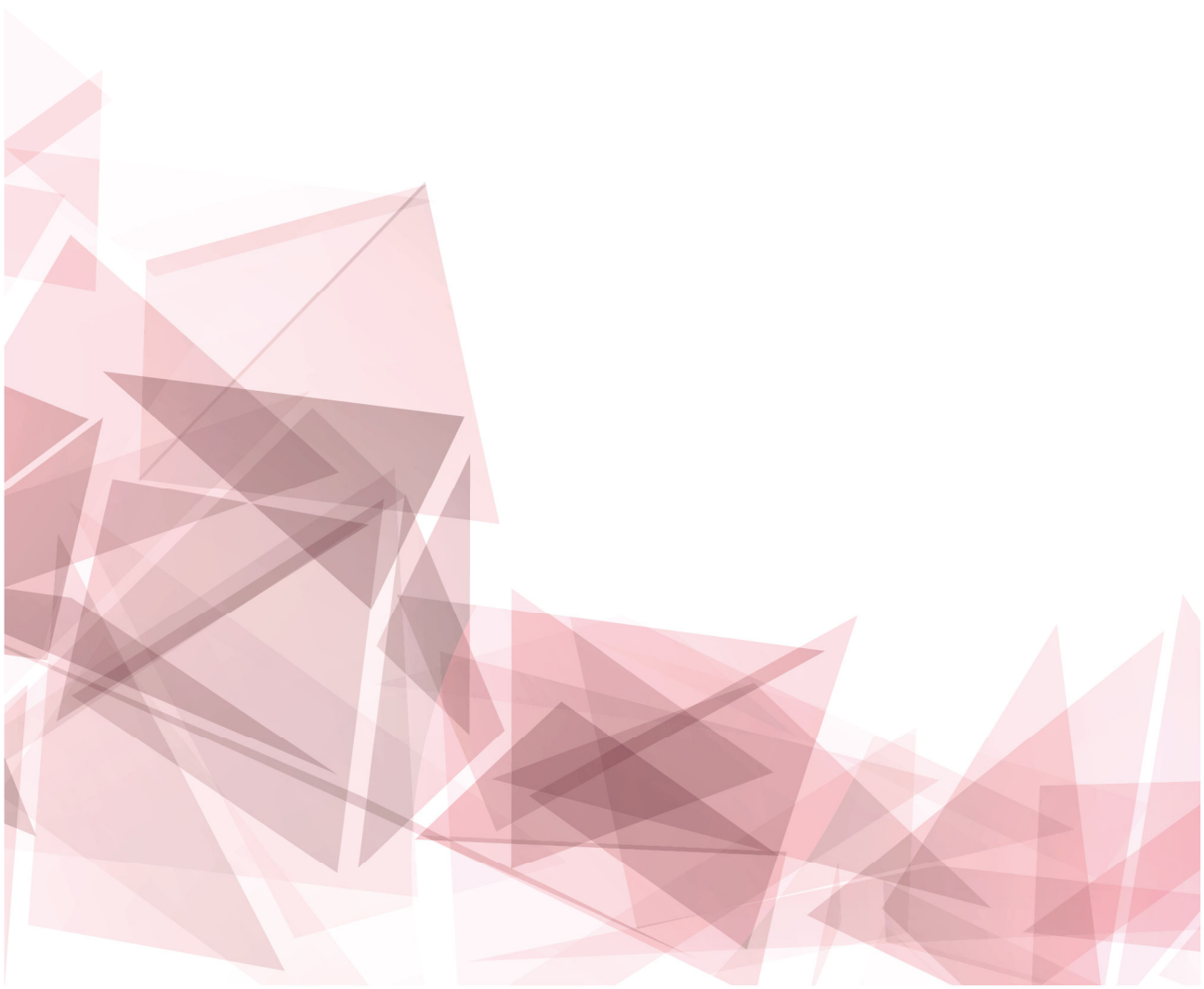

Chapter 1

General introduction and outline of this thesis

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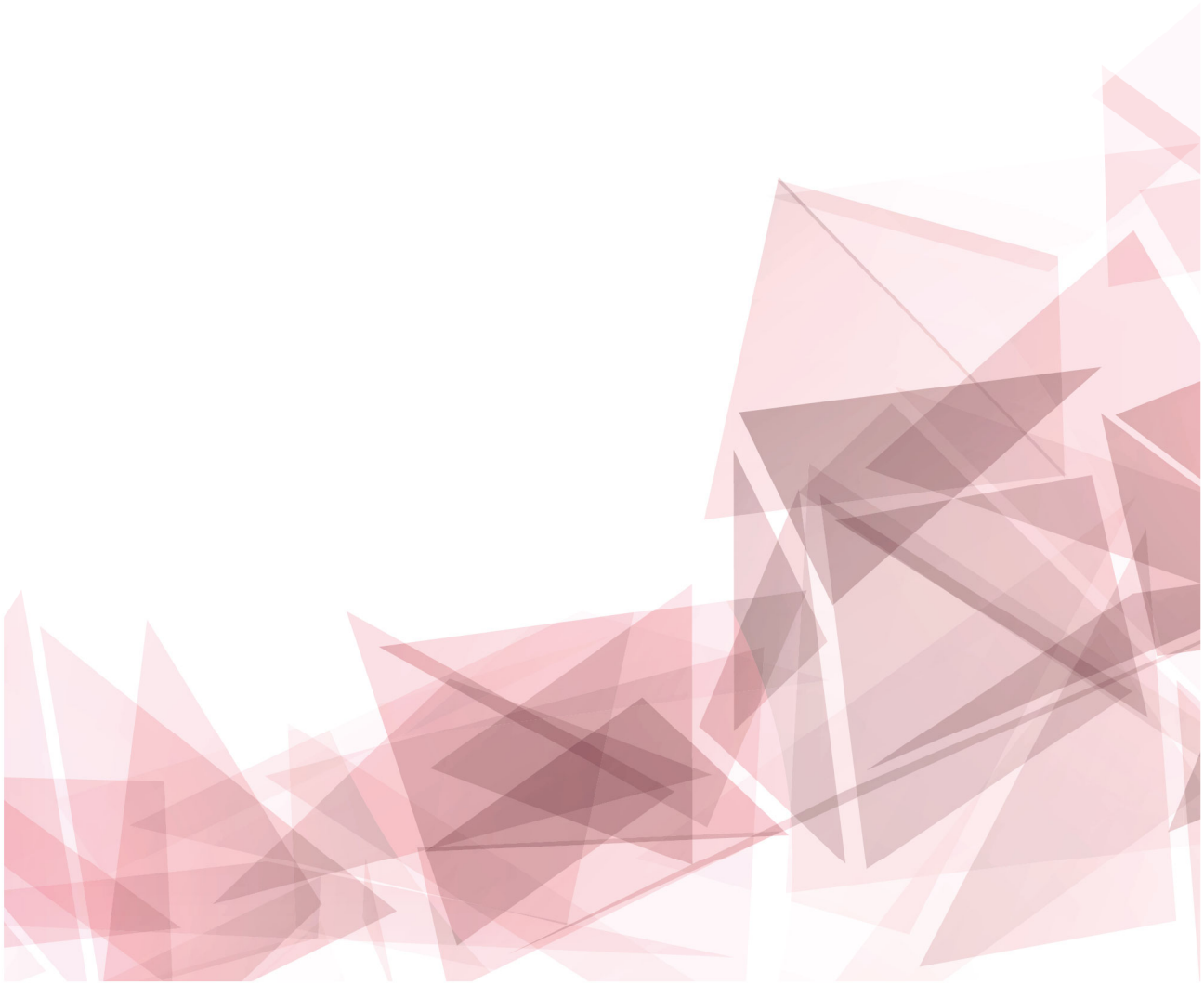
Eur Resp Rev. 2020;29(156):190139



Chronic obstructive pulmonary disease and acute myocardial infarction

Chronic obstructive pulmonary disease (COPD) is a clinical syndrome characterized by chronic respiratory symptoms, structural pulmonary abnormalities, impaired lung-function (mainly progressive airflow limitation with poor reversibility) or any combination of these.[1] In 2010, more than 300 million people were estimated to suffer from this disease worldwide and it has become the third leading cause of death.[2] Although COPD was originally thought to merely affect the airways and lungs, the attention of research has been shifted towards the high prevalence of cardiovascular disease in patients with COPD.[3] Up to one third of deaths in patients with COPD can be attributed to a cardiovascular cause, illustrating the major impact of this comorbidity.[4] In particular, a strong association between COPD and acute myocardial infarction (AMI) has been emphasized and the need for adequate risk stratification in this population has been recognized as an unmet clinical need.

Identification of patients at risk of adverse events after AMI is frequently performed with cardiac imaging.[5, 6] Echocardiography permits early assessment of left- and right ventricular size and function, as surrogates of cardiac damage in the acute phase. Emerging advanced echocardiographic techniques such as speckle tracking strain imaging enable characterization of myocardial mechanics (strain and mechanical activation time dispersion) which have been associated with hard endpoints such all-cause and cardiac mortality, heart failure hospitalization and ventricular arrhythmias.[7, 8] Additionally, cardiac magnetic resonance imaging (CMR) provides more information on tissue characterization useful to predict future cardiac remodeling and development of arrhythmias.[9] The present article reviews (i) the pathophysiologic factors involved in the interaction between COPD and AMI, (ii) the prevalence and outcomes of AMI in patients with COPD and (iii) the role of imaging in the acute phase and risk stratification after AMI in patients with COPD.

Acute myocardial infarction in patients with COPD

Mechanisms

Several pathological mechanisms underlie the relationship between COPD and ischemic heart disease (IHD). First, COPD and IHD share common risk factors of which smoking and increasing age are most important. Moreover, the prevalence of other cardiovascular risk factors such as diabetes and hypertension seems to be higher in patients with COPD as compared to healthy individuals.[10] Besides shared risk factors, COPD specific characteristics are important features in the interaction with IHD. Although COPD is primarily characterized by local inflammation of the lungs, a spill-over to systemic inflammation has been shown in previous studies by increased levels of proteins in the acute phase (i.e. interleukin-6, C-reactive protein and fibrinogen).[11, 12] These factors are involved in the atherosclerotic process inducing plaque formation and growth. Another consequence of

systemic inflammation in patients with COPD is an increased platelet count and reactivity, increasing the risk of thrombotic events. Moreover, increased levels of coagulation factors are reported in patients with COPD, resulting in higher thrombin levels.[13] In addition, high levels of matrix metalloproteinases (MMP's) have been reported which increase the risk of atherosclerotic plaque formation, destabilization and rupture, thrombus formation and increased arterial stiffness.[14] At follow-up, increased levels of MMP's have been related to left ventricular (LV) remodeling after AMI.[15] Furthermore, COPD related hypoxia has been associated with activation of the renin-angiotensin system leading to reduced renal blood flow and peripheral vasoconstriction and to increased oxidative stress which eventually increases the risk of AMI. A schematic overview of the complex interaction between COPD and IHD based on current knowledge is displayed in Figure 1.

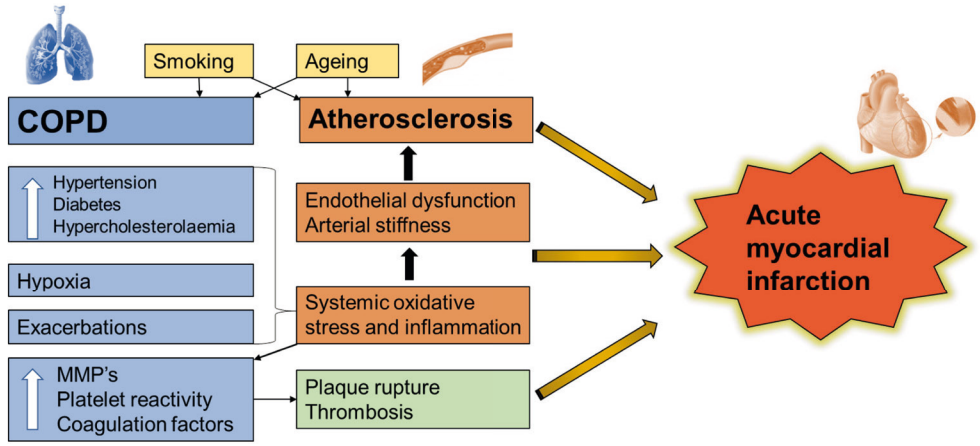


Figure 1. Schematic overview of the mechanisms involved in the interaction between COPD and acute myocardial infarction.

Prevalence

In previous literature, the prevalence of COPD in study populations consisting of patients with AMI ranges between 7% and 28%.[16-24] These studies used different definitions for the diagnosis of COPD leading to variable prevalence and limited generalizability. In the few studies performing standardized pulmonary functional tests in patients with coronary artery disease, the prevalence of COPD was as much as 30% and the majority of the patients were newly diagnosed.[25-27] Therefore, it is likely that the prevalence of COPD in patients with AMI is underestimated in most registries, due to a large number of undiagnosed patients. In a British registry of more than 1 million patients (among those, 29,870 patients had COPD) attending to primary care facilities, the prevalence of AMI was 3.5 times higher in patients with COPD as compared to patients without COPD (HR 3.53, 95% CI 3.02 – 4.13).[28] A similar study performed by Schneider et al. followed 35,772 patients with COPD from the moment of COPD diagnosis and an equal number of patients without COPD for incident

cardiovascular disease during follow up.[29] The relative risk estimate for incident AMI was 1.40-fold higher among patients with COPD compared to patients without COPD.[29] This relative risk increased up to 3.00 (95% CI 1.53 – 5.86) for patients with severe COPD.[29]

Influence of acute exacerbations

COPD is often accompanied by recurrent episodes of acute exacerbation, mostly caused by viral respiratory infections and leading to hospital admissions.[30] Acute exacerbations of COPD lead to an increased systemic inflammatory response, thereby increasing the risk of cardiovascular events through some of the pathways before mentioned.[12, 31] Previous studies in patients with COPD admitted for acute exacerbation, showed increased levels of troponin T in a considerable part of the study population.[32, 33] Whereas not all these patients indeed have AMI, a Chinese study by Wang et al. aimed to find a new cut-off value for high-sensitive troponin T (hs-TnT) in patients with COPD presenting with acute exacerbation.[34] They propose a cut-off value of 60.5 ng/l to diagnose AMI in this patient group, which is substantially higher compared to the normal reference population (14 ng/l).[34] However, this cut-off value has not been validated in other studies. Moreover, McAllistar et al. demonstrated that 24 (10%) patients admitted for COPD exacerbation had increased troponin levels of whom 20 (8.3%; 95% CI 5.1 – 12.5%) also had chest pain and/or ECG changes meeting the criteria for AMI.[35] It is thought that most of these AMI events are type 2 AMI (oxygen supply-demand imbalance) induced by tachycardia, hypoxia and an increased afterload.[35] Interestingly, in 88 patients admitted for acute exacerbation of COPD with elevated Troponin I levels, invasive coronary angiography demonstrated significant coronary artery disease in 67% and in 38.6% percutaneous coronary intervention was performed.[36] The patients requiring percutaneous intervention had significantly worse LV function and more frequently ST-segment depression on the ECG, although in 23 patients requiring intervention these echo- and electrocardiographic indices of ischemia were absent.[36] This study indicates that not only type 2 AMI occurs in patients with COPD with acute exacerbation and elevated Troponin levels. However, the value and interpretation of elevated Troponin levels in patients presenting with acute exacerbation of COPD remains a subject of debate. Further research to provide a diagnostic strategy in these patients is warranted.

Not only during admission for acute exacerbations but also during follow-up, the risk of AMI is increased in patients with COPD. A study by Campo et al., including patients admitted with an acute exacerbation of COPD, demonstrated that elevated Troponin T levels during admission tripled the risk of non-fatal AMI during follow-up and doubled the risk of cardiovascular death as compared to patients without elevated Troponin levels.[32] A similar trend has been described in stable patients with moderate COPD and coexisting CV disease or increased CV risk.[37] In a substudy of the Study to Understand Morbidity and Mortality (SUMMIT), patients with the highest quintile of Troponin I obtained before randomization (≥7.7 ng/l) had a >3.5 times higher risk of a composite CV event as

compared to patients within the lowest quintile (<2.3 ng/l) (HR 3.67, 95%CI 1.33-10.13; p=0.012).[37]

Outcomes after AMI in patients with COPD

Mortality

Prognosis of patients with COPD after AMI is markedly worse as compared to patients without COPD, both during short- and long-term follow-up (Table 1). Particularly, all-cause mortality rates are significantly higher after correcting for known prognostic factors and smoking. In a large population based registry in the United Kingdom, including 34,019 patients with COPD and 266,142 patients without COPD, the 6-months mortality rates were significantly higher among patients with COPD and non-ST-segment elevation myocardial infarction (non-STEMI) and ST-segment elevation myocardial infarction (STEMI) as compared to patients without COPD (adjusted HR 1.26; 95% CI 1.17 – 1.35 and HR 1.25; 95% CI 1.11 - 1.41, for non-STEMI and STEMI, respectively).[20] These results were confirmed in subsequent studies reporting double mortality rates for COPD patients as compared to patients without COPD at long follow-up (Table 1).[16, 21, 38]

Heart failure

Although it is known that patients with COPD have an increased risk of heart failure development, only few studies address heart failure hospitalization after AMI in this subgroup of patients. A sub-study of the Valsartan in Acute Myocardial Infarction Trial (VAILANT) including 1,258 COPD and 13,445 non-COPD patients, demonstrated that COPD was an independent predictor of heart failure hospitalization during follow-up (HR 1.19, 95% CI 1.05-1.34).[19]

Arrhythmias

Cardiac arrhythmias, both supraventricular and ventricular, are common in patients with COPD.[3, 39] Data on the risk of arrhythmias after AMI associated with COPD are scarce. A meta-analysis of 4 randomized clinical trials, including 26,436 non-STEMI patients and a history of COPD showed that COPD was an independent predictor of in-hospital ventricular arrhythmias (OR 2.5; 95% CI1.6 – 4.1 and OR 1.9; 95% CI 1.1 – 3.1 for ventricular tachycardia and ventricular fibrillation, respectively).[40] Similarly, sub-analysis of the VALIANT trial reported an increased risk of sudden cardiac death (SCD) during follow-up after AMI (STEMI and non-STEMI) for COPD patients compared to patients without COPD (HR 1.26; 95% CI 1.03 - 1.53).[19]

Table 1. Studies assessing the outcomes of patients with COPD after acute myocardial infarction.

Study	Year of publication	No. of patients	MI type	Primary endpoints	Follow-up	Mortality*	Heart failure hospitalization*	Arrhythmias*
Al-Khatib et al.[40]	2002	26,463	Non-STEMI	In-hospital VT and/or VF and associated 30-day and 6 months mortality	6 months	NA	NA	In-hospital VT: OR 2.5 (95% CI 1.6 - 4.1) In-hospital VF: OR 1.9 (95% CI 1.1 – 3.1)†
Selvaraj et al.[16]	2005	1,117 COPD vs. 9,877 No COPD	Stable angina, unstable angina, acute MI	All-cause mortality	Mean 34 months	Adjusted HR 2.16 (95% CI 1.81 – 2.56	NA	NA
Salisbury et al.[38]	2007	387 COPD vs. 2,094 No COPD	STEMI and non-STEMI	All-cause mortality	12 months	Adjusted HR 2.00 (95% CI 1.44-2.79)	NA	NA
Hawkins et al.[19]	2009	1,258 COPD vs. 13,445 No COPD	STEMI and non-STEMI	All-cause mortality	Median 24.7 months	Adjusted HR 1.14 (95% CI 1.02-1.28)	Adjusted HR 1.19 (95% CI 1.05-1.34)	SCD: Adjusted HR 1.26 (95% CI 1.03-1.53)
Bursi et al.[22]	2010	415 COPD vs. 3,039 No COPD	STEMI and non-STEMI	All-cause mortality	Mean 4.7 ± 4.6 years	Adjusted HR 1.30 (95%CI 1.10 – 1.54)	NA	NA
Lazzeri et al.[21]	2011	71 COPD vs. 747 No COPD	STEMI	All-cause mortality	Median 37.3 [IQR 17.8-53.8] months	Adjusted HR 2.40 (95% CI 1.36 - 4.25)	NA	NA
Enriquez et al.[18]	2011	860 COPD vs. 10,048 No COPD	Stable angina, unstable angina, acute MI	Composite of death, MI and repeat revascularization	1 year	Adjusted HR 1.30 (95% CI 1.01 – 1.67)	NA	NA
Stefan et al.[43]	2012	1,080 COPD vs. 5,210 No COPD	STEMI and non-STEMI	All-cause mortality	In-hospital and 30 days	30 days: Adjusted HR 1.31 (95% CI 1.10-1.85)	In hospital: Adjusted OR 1.59 (1.37-1.83)	Atrial fibrillation: Adjusted OR 1.14 (0.97-1.34)
Campo et al.[17]	2013	2,032 COPD vs. 9,086 No COPD	STEMI	All-cause mortality	3 years	Adjusted HR 1.4 (95% CI 1.2-1.6)	COPD 25% No COPD 17% P<0.01	NA
Rothnie et al.[20]	2015	34,019 COPD vs. 266,142 No COPD	STEMI and non- STEMI	All-cause mortality	180 days	Adjusted OR for STEMI patients: 1.25 (95% CI 1.11 – 1.41)	NA	NA
Tse-Hsuan et al.[23]	2017	1,921 COPD vs. 4,849 No COPD	STEMI and non-STEMI	All-cause mortality	NA	1 year mortality: Adjusted HR 1.20 (95% CI 1.01 - 1.32)	NA	NA
Agarwal et al.[45]	2017	279,488 COPD vs 1,840,517 No COPD	STEMI	In-hospital mortality	NA	Adjusted OR 1.13 (95%CI1.11 – 1.15)	New-onset HF Adjusted OR 2.01 (95%CI 1.99-2.03)	NA
Serban et al.[82]	2017	31 COPD vs. 387 no COPD	STEMI	Multiple in-hospital outcomes		In-hospital mortality adjusted OR 2.80 (95%CI 0.82-4.96)		Atrial fibrillation: adjusted OR 1.56 (95%CI 0.39-6.31) VT/VF: adjusted OR 1.40 (95%CI 0.44-4.48)

*Outcomes are displayed as adjusted hazard ratio or odds ratio (95% confidence interval) for patients with COPD as compared to patients without COPD, when available. † Odds ratio representing the presence of COPD as an independent predictor for the occurrence of in-hospital VT or VF.

In summary, the evidence on the detrimental impact of COPD on the outcome of patients experiencing AMI is accumulating. Although the exact pathophysiologic mechanisms are still largely unexplained, the need for adequate risk stratification to identify patients at risk for adverse events has been recognized as unmet clinical need. The next sections of this review will focus on early recognition and treatment of patients with AMI and concomitant COPD and the role of imaging in the risk stratification.

Unmet clinical needs in diagnosis and treatment of COPD patients with AMI

Early detection

Part of the differences in outcome between COPD and non-COPD patients could be explained by the diversity in clinical presentation, delaying diagnosis of AMI and leading to greater infarct size. Difficulties in recognizing AMI in patients with COPD have been acknowledged in previous studies. Patients with COPD more often present with atypical chest pain or dyspnea at the emergency room. In a large population of consecutive patients with AMI admitted to coronary care units in Sweden, 1,092 out of 4,867 COPD patients (22.5%) presented with dyspnea as opposed to 5,429 out of 76,324 non-COPD patients (7.1%).[41] A similar rate of COPD patients presenting with dyspnea was observed by Hadi et al.[42] and in a retrospective study performed by Stefan et al.[43] >60% of COPD patients with AMI presented with dyspnea. Furthermore, COPD patients more often present with non-STEMI or unstable angina instead of STEMI as compared to non-COPD patients, increasing the risk of misdiagnosis and delayed intervention.[19, 38, 41, 43, 44]

Controversy in treatment

A possible consequence of misleading symptoms in COPD patients with AMI is delayed reperfusion and subsequent greater infarct size and/or worse prognosis. This was demonstrated by Rothnie et al [20] with a median of 43.7 minutes longer time to reperfusion among COPD patients as compared to non-COPD patients, both with delayed diagnosis of AMI. After adjustment for several factors, the difference in time to reperfusion remained 47% longer for COPD patients with delayed diagnosis of AMI as compared with their counterparts (95% CI 15% to 88%). In contrast, a large Swedish study including 81,191 patients with AMI showed that COPD patients were less likely to arrive at the coronary-care unit within 12 hours after symptom onset (84% vs. 87.4%; $p<0.001$) as compared to non-COPD patients but still the rate of patients with percutaneous coronary intervention (PCI) within 12 hours after symptom onset was similar for both groups of patients (91.1% vs 91.9%, $p=0.488$).[41] This was confirmed in a smaller STEMI population comparing 71 COPD patients with 747 non-COPD patients, demonstrating similar door-to-balloon time in the two groups (median 180 [IQR 140 – 360] minutes vs. 230 [IQR 160 – 303] minutes; $p=0.314$, for COPD and non-COPD patients, respectively).[21] Therefore, convincing evidence for delayed intervention in COPD patients as compared to patients without COPD is lacking,

although comparison of the above mentioned studies should be performed with caution due to differences in study populations.

While controversy in literature exists with regard to delayed reperfusion treatment in COPD patients as compared to patients without COPD, recent studies recognize lower rates of immediate intervention in AMI patients with COPD. At the moment of presentation, patients with COPD are less likely to receive diagnostic angiography or PCI when compared to patients without COPD.[20, 22, 41, 45] The factors related to the hesitation for invasive diagnostics and/or treatment in COPD patients presenting with AMI have not been elucidated. A possible explanation is that COPD patients are deemed to be older with higher frailty, which could lead to hesitation for aggressive treatment.

Besides invasive treatment strategies, controversy exists on pharmacological treatment after AMI in patients with COPD. Particularly the use of β-blockers has been a subject of debate in many studies and clinical practice. Evidence is accumulating in favor of the use of β-blockers in patients with COPD in terms of safety and mortality reduction, but clinicians still seem to be reluctant to prescribe these drugs in this particular population due to the fear of bronchoconstriction or pulmonary function decline. For example, a study considering 1,573 high-risk AMI survivors with concomitant COPD evaluated the influence of β-blocker use on long-term survival.[46] Their results demonstrate that β-blocker use was associated with better outcome in terms of all-cause and cardiovascular mortality (HR 0.73, 95%CI 0.60-0.90, p=0.003 and HR 0.77, 95%CI 0.61-0.97, p=0.025, respectively).[46] Similar results were demonstrated in a prior population study by Quint et al. including COPD patients with first AMI (n=1,036).[47] Although only 38% of the patients were prescribed a β-blocker, after a median follow-up of 2.9 years there was a clear survival benefit for patients using a β-blocker initiated at the admission for AMI as compared to patients in whom β-blockers were not prescribed (HR 0.50, 95% CI 0.36 – 0.69).[47] Despite the evident survival benefit of using β-blockers in COPD patients after AMI, observational studies considering infarction populations report a 4% to 30% lower rate of β-blocker prescription at discharge in COPD patients as compared to patients without COPD.[17, 19-22, 38, 41, 43, 44] As to be expected, this topic will continue to be a subject of debate both in COPD patients with IHD as well as heart failure.

Guideline based secondary prevention in AMI patients with COPD

Besides β-blockers there are several other medications of importance for preventing future cardiovascular events after AMI, such as antiplatelet drugs, statins and ACE inhibitors or angiotensin II receptor blockers (ARB's). Numerous reviews have been written about the management of cardiovascular risk or cardiovascular disease in COPD patients.[48-50] Although many studies regarding the effect of such medications concern COPD patients without overt cardiovascular disease, few registries, post hoc analysis and observational studies are indicating to treat patients with CVD and concomitant COPD not any different

in terms of secondary cardiovascular prevention.[49] A brief summary of available literature on this subject is presented in Table 2.

Table 2. Secondary prevention in COPD patients with cardiovascular disease.

Study	Year of publication	No. of patients	Type of medication studied	Main results
Mancini et al.[83]	2006	High risk cohort of patients after coronary revascularization: N=946 COPD patients using studied medication N=18,774 COPD patients not using studied medication	Statins ACE inhibitors ARB's	*ARB's reduce risk of:* -Death: RR 0.62 (95%CI 0.44-0.87) -MI or death: RR 0.71 (95%CI 0.56-0.89) *Statins reduce risk of:* -COPD hospitalization RR 0.71 (95%CI 0.56-0.90) -MI: RR 0.48 (95%CI 0.39-0.59) -Death: RR 053 (95%CI 0.43-0.65) -MI or death: RR 0.50 (95%CI 0.43-0.58) *ACE inhibitor reduce risk of:* -MI: RR 0.72 (95%CI 0.59-0.87) -MI or death: RR 0.75 (95%CI 0.64-0.86)
Sheng et al.[84]	2012	COPD patients with established CV disease N=292 with statin use N=151 without statin use	Statins	Recurrent CV event: Adjusted HR 0.35 (95%CI 0.15-0.87) CV mortality: Adjusted HR 0.32 (95%CI 0.13-0.77)
Andell et al.[44]	2015	N=1085 COPD N=17,528 no COPD	Ticagrelor vs. Clopidogrel	-Composite CV endpoint: Ticagrelor vs. Clopidogrel HR 0.72 (95%CI 0.54-0.97) for COPD patients -Relative risk for ticagrelor related dyspnea 1.71 (95%CI 1.28-2.30) in COPD and 1.85 (95%CI 1.68-2.04) in non-COPD patients (p for interaction 0.616)

ACE; angiotensin converting enzyme, ARB; angiotensin II receptor blocker, CI; confidence interval, COPD; chronic obstructive pulmonary disease, CV; cardiovascular, MI; myocardial infarction, RR; risk ratio

Risk stratification: role of cardiac imaging

Since the risk of adverse events (e.g. reinfarction, heart failure or death) after AMI is most substantial shortly after the index event and decreases over time, early risk assessment is warranted.[5] Risk assessment after AMI commences with evaluation of infarct size and resting LV function before hospital discharge. In addition to biomarkers (i.e. cholesterol, troponin, creatine phosphokinase), several imaging techniques are currently available for risk stratification. For evaluation of LV function and infarct size, transthoracic echocardiography is the most suitable and readily available imaging technique. Repeated evaluation of LV ejection fraction (LVEF) is appropriate for selection of patients requiring implantation of an internal cardioverter-defibrillator (ICD) for primary prevention. Recently, novel imaging techniques such as speckle tracking echocardiography have emerged for assessment of atrial and ventricular deformation (strain imaging) and electrical conduction heterogeneity (mechanical dispersion). The next sections of this

review will discuss evaluation of i) LV size and function, ii) right ventricular (RV) systolic function and iii) novel imaging techniques emerging for risk stratification after AMI, focusing on patients with concomitant COPD.

Left ventricular size and function

Assessment of LV function by using LVEF has a class I recommendation in STEMI guidelines.[5] LVEF predicts early all-cause mortality and SCD after AMI and has a role in therapeutic management. Besides LVEF, wall motion score index (WMSI) is a frequently used measure of systolic function after AMI.[51] For assessment of LV size and function, echocardiography remains the most widely used technique, due to its availability, lack of radiation exposure and relatively low cost. However, CMR is still considered the gold standard.[52] The advantage of CMR over echocardiography is its low inter- and intra-observer variability. Another disadvantage of echocardiography are the poor acoustic windows in patients with obesity and/or COPD. Despite the advantages of CMR, the limited availability, high costs and time-consuming examination and post-processing still lead to the preference of echocardiography in the setting of AMI. This is also stated in the most recent STEMI guidelines with a class IIb recommendation for CMR as an alternative to echocardiography.[5]

As for patients with COPD, limited imaging studies have been performed in subpopulations with AMI. Conflicting results are described whether or not COPD patients have worse LVEF after STEMI, as compared to patients without COPD.[17-19, 21, 24, 38] A retrospective cohort comparing 133 STEMI patients with COPD to 1,617 STEMI patients without COPD demonstrated similar infarct size using conventional parameters such as LVEF and WMSI.[24] However, advanced echocardiographic parameters indicated greater infarct size in COPD patients (Figure 2).[24] In another large STEMI registry including 11,118 patients of which 2,032 had a history of COPD, the percentage of patients with LVEF<35% was significantly higher amongst COPD patients as compared to their counterparts (15% vs. 12%, respectively, $p<0.01$). This is of particular interest since LVEF≤35% is the main indication for ICD implantation.[53] Furthermore, in a sub-study of the VALIANT trial including patients with AMI complicated with heart failure and/or LV dysfunction, the impact of COPD on clinical outcome was investigated.[24] Although similar LVEF values were observed in COPD patients compared to non-COPD patients (34% vs. 35.4%, respectively, $p>0.05$), the risk of SCD was significantly higher in COPD patients (adjusted HR 1.26, 95% CI 1.03-1.53, $p = 0.025$).[19] This stresses the need for better characterization of the substrate for SCD in these patients.

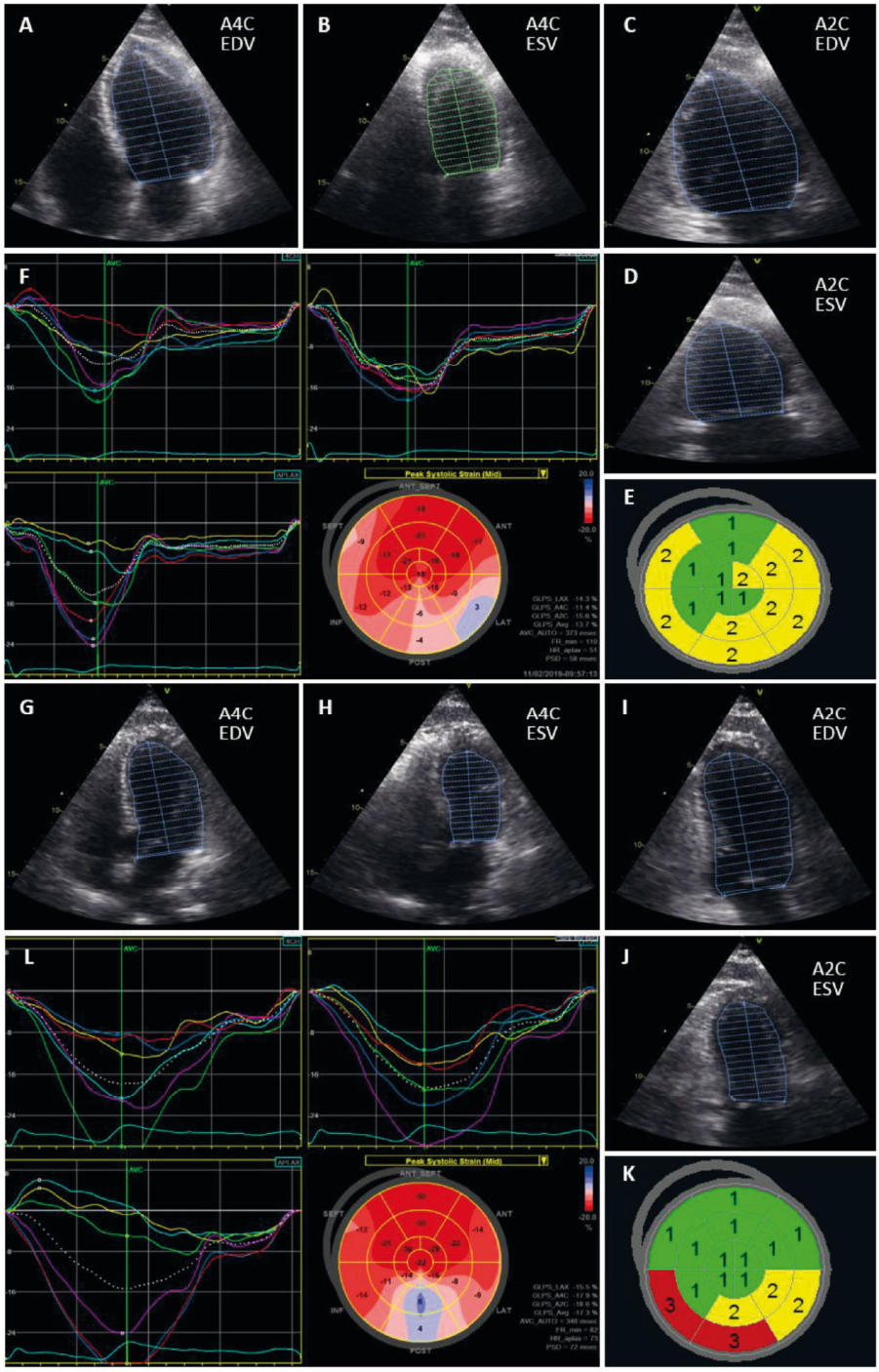


Figure 2. Left ventricular volume and function assessment with echocardiography. Example of two patients after ST-segment elevation myocardial infarction with COPD (A-F) and without COPD (G-L).

Only few CMR studies have been performed in patients with COPD, mainly focusing on patients without overt cardiovascular disease and mostly assessing the right side of the heart. Furthermore, CMR studies in AMI patients rarely mention the presence of COPD as a comorbidity in their patient populations and/or have small numbers.[54] This leaves a gap in knowledge on scar characterization in patients with COPD.

Few studies have described smaller LV size in COPD patients without overt cardiovascular without impairment of LV function.[55, 56] Whether LV remodeling post-infarction is different in COPD patients compared to patients without COPD, has not been described before. This could be of interest to further elucidate the mortality risk and heart failure development in COPD patients after AMI.

Right ventricular systolic function

RV involvement in AMI has long been neglected and overshadowed by the importance of LV dysfunction. The awareness of the influence of RV systolic dysfunction on clinical status and prognosis after AMI has increased in the last decade. RV involvement is predominantly present in inferior AMI caused by proximal right coronary artery occlusion with a prevalence up to 30% depending on the diagnostic parameter used.[57, 58] Previous studies have recognized the prognostic implications of RV dysfunction after AMI both in patients with inferior and anterior MI.[57, 59, 60]

Assessment of RV systolic function is challenging due to the complex RV geometry. In patients with AMI, CMR and echocardiography have contributed significantly to the understanding and evaluation of RV involvement. Although CMR remains the gold standard for RV systolic function assessment, various echocardiographic parameters are currently available to assess RV function in a bedside manner (Figure 3A-C). Tricuspid annular plane systolic excursion, fractional area change and novel techniques such as RV strain are of important prognostic value in AMI, independently of LV function.[59]

Although the RV is less vulnerable to ischemia than the LV due to a more balanced oxygen supply and demand, this might be affected when RV hypertrophy or pulmonary hypertension is present.[61] In the normal situation, the thin walled RV only has to perform little effort to create stroke volume into the low-resistance pulmonary vascular circulation. This changes when pulmonary hypertension is present leading to an increase in the oxygen demand of the RV and changes in the coronary flow which then makes the RV more susceptible for ischemia.[61-63] In patients with COPD, RV hypertrophy has shown to be present even in the absence of pulmonary hypertension. In a CMR study assessing 25 patients with COPD without evidence of pulmonary hypertension, RV mass was significantly higher as compared to 26 healthy controls (68±12 gram vs. 59±14 gram; $p<0.01$).[64] This was also found in a study by Sabit et al. using echocardiography to assess LV and RV structure and function in 36 COPD patients free of overt cardiovascular disease, compared with 14 current or ex-smokers.[65] Particularly, greater RV free wall thickness and impaired RV systolic function based on tricuspid annular peak systolic velocity, RV strain

and Tei index were demonstrated in COPD patients.[65] These differences were observed in both patients with mild airflow obstruction and more diseased patients with evidence of pulmonary hypertension. These studies indicate the presence of RV remodeling and subclinical dysfunction in early stages of COPD, before overt cardiac disease.

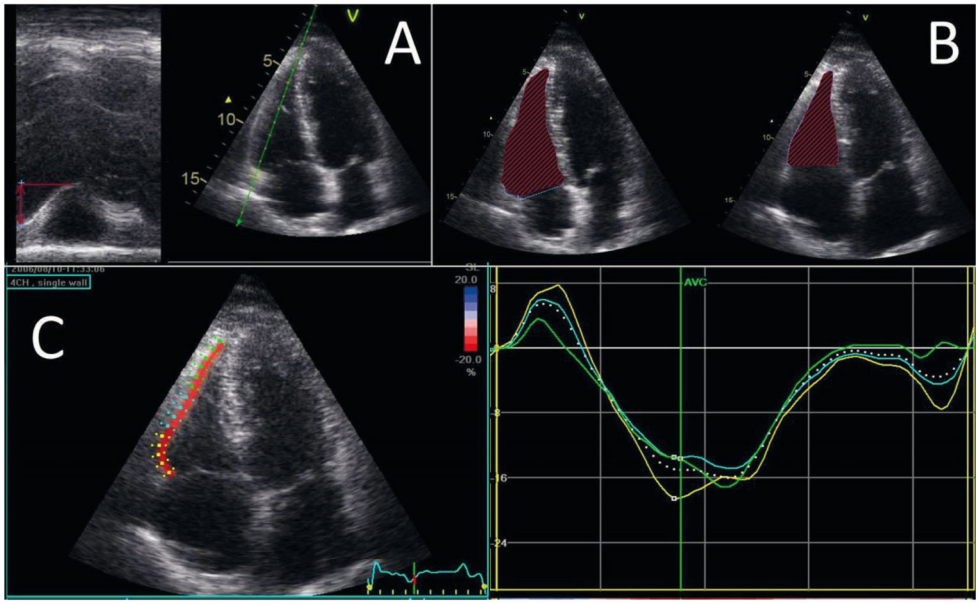


Figure 3. Right ventricular systolic function assessment in a ST-segment elevation myocardial infarction patient with chronic obstructive pulmonary disease. Example of a patient with normal right ventricular (RV) systolic function when assessed with conventional parameters such as tricuspid annular plane systolic excursion (TAPSE; panel A) or fractional area change (FAC; panel B), but impaired RV systolic function when assessed with advanced speckle tracking echocardiography (free wall strain longitudinal [FWSL]; panel C).

Studies concerning the assessment of RV systolic function after AMI in patients with COPD are lacking. In addition, although the general population frequently show RV functional recovery after AMI, this remains unknown among COPD patients who might already have subclinical damage.[66] Therefore, future research on this subject is required in order to elucidate the influence of COPD on RV function after AMI and the subsequent prognostic implications.

The advent of CMR is the ability to visualize the three-dimensional RV anatomy and function but the availability is limited, especially in the acute setting. Echocardiography is an easily available imaging technique and nowadays various parameters are available for assessment of RV systolic function. However, the complex geometry of the RV makes assessment of RV dimensions and function with echocardiography more challenging as compared to the LV.

Novel imaging markers for risk stratification

Speckle tracking echocardiography. Besides conventional echocardiography, LV function can be assessed using speckle tracking echocardiography (Figure 4A). This enables measurement of active deformation (strain) of the myocardium, either longitudinal, circumferential or radial. Global longitudinal strain (GLS) has been thought to indirectly represent myocardial fibrosis or scar, and has been associated with prognosis in various cardiac diseases. In STEMI patients, GLS has been independently associated with increased all-cause mortality, cardiovascular mortality, heart failure, SCD and appropriate ICD therapy.[7, 8, 67] Interestingly, in a retrospective study including 143 STEMI patients with COPD, GLS was independently associated with all-cause mortality and a combined endpoint including all-cause mortality and heart failure admission.[68] In addition, GLS had incremental value over conventional LVEF and TAPSE.[68] Therefore, GLS might serve as a better marker for risk stratification after STEMI in patients with COPD as opposed to conventional measures for LV and RV function. Myocardial strain assessment can also be performed by CMR, using several techniques. However, convincing evidence on the prognostic value of CMR derived myocardial strain after STEMI is lacking due to limited studies with small populations and conflicting results.[69]

In addition to GLS, speckle tracking echocardiography can be used to assess the time to peak longitudinal strain in each of the 17 LV segments. The standard deviation of these 17 segments, so-called mechanical dispersion (MD), represents the heterogeneity of electrical conduction in the myocardium (Figure 4C). Increased LV MD has been associated with increased risk of SCD and/or ventricular arrhythmias in patients after STEMI, heart failure patients receiving cardiac resynchronization therapy but also in hypertrophic cardiomyopathy patients where MD was also associated with myocardial fibrosis.[67, 70, 71] The Rotterdam study, a population-based cohort study among 14,926 subjects, demonstrated a >30% increased risk of SCD in patients with COPD, especially in persons with frequent exacerbations.[72] Additionally, another study has indicated an increased risk of ventricular arrhythmias in patients with COPD, irrespective of LVEF.[73] However, the pathophysiology behind this pro-arrhythmogenicity has not been completely elucidated, for which assessment of MD could be of additional value.

Atrial mechanics. The importance of left atrial (LA) volume and function as markers of adverse events after AMI has emerged in the last decade.[74, 75] LA volume is considered to represent LV diastolic function and increased LA volume can arise from chronic increased LV filling pressures. An AMI can result in (worsening of) diastolic dysfunction and subsequent LA remodeling. The evidence suggests that this process starts early after AMI and can deteriorate over time, leading to worse prognosis.[74, 75] Diastolic dysfunction frequently occurs in patients with COPD, partly due to hyperinflation leading to impaired LV filling.[76] Therefore LA volume overload might be unlikely in COPD patients. However, the

chronic systemic inflammatory status and frequently occurring pulmonary hypertension might lead to atrial remodeling, resulting in decreased atrial function.[39]

Besides LA volume, determination of LA function has proven to be of additional value in predicting adverse events after AMI.[77] Analysis of LA function can be performed using conventional echocardiography as well as speckle tracking (Figure 4B). Atrial function can be divided into the reservoir phase (during ventricular systole), conduit phase (passive emptying during ventricular relaxation) and the contractile phase (active emptying).[77] In a retrospective study concerning 320 AMI patients, LA reservoir strain was independently associated with a composite of all-cause mortality, reinfarction and hospitalization for heart failure (HR 0.94, 95% CI 0.89 – 0.99, p = 0.02). More recently, Nourian and colleagues measured right atrial strain in 70 patients with inferior myocardial infarction.[78] Right atrial reservoir and conduit functions were impaired in patients with RV infarction as compared with patients without RV infarction.[78] Whether right atrial strain has prognostic implications, has not been investigated.

In general, speckle tracking echocardiography allows evaluation of the active deformation of the myocardium in multiple directions which is less angle- and volume dependent in comparison with measurements used in conventional echocardiography. A disadvantage are the inter-vendor differences originating from different software algorithms, limiting comparison of results obtained in studies to create generally applicable cutoff values.

T1 mapping. Whereas CMR imaging with late gadolinium enhancement (LGE) is considered the gold standard for measurement of infarct size after AMI, post-contrast T1 mapping has recently emerged as new CMR technique. Few studies have demonstrated that native T1 mapping can accurately quantify infarct size and the edema-based area at risk when compared with conventional T2 mapping and LGE imaging (Figure 4D).[79, 80] Also, T1 mapping has been identified as a strong predictor of LV remodeling post-infarction.[80] This promising technique could potentially shorten scanning time substantially, making CMR a more suitable imaging technique in STEMI patients. Interestingly, a pilot CMR study was performed in patients with COPD, free of overt cardiovascular disease, using T1 mapping to assess myocardial extracellular volume (ECV) as a measure of cardiac fibrosis.[81] In the 8 COPD patients, an increased ECV was observed when compared with healthy controls (median 0.32 vs. median 0.27, p=0.001). This was associated with LV remodeling, reduced LA function and reduced exercise capacity.[81] Although this was a small pilot study, the results indicate the feasibility of T1 mapping in COPD patients to detect signs of cardiac fibrosis related to clinical status.

The benefit of T1 mapping over conventional T2 mapping and LGE imaging could be a significant shortening in acquisition time which is particularly valuable in AMI patients. However, T1 mapping has only been tested in a few small studies concerning patients with first AMI and the value of T1 mapping in patients with previous MI has to be determined.

In summary, echocardiography remains the most widely used imaging technique for risk stratification after AMI. Advanced echocardiographic parameters have already provided new insights in the prognosis of AMI patients, but further research is still needed. Although imaging studies in AMI patients with concomitant COPD are scarce, studies evaluating cardiac function in COPD patients indicate the presence of cardiac dysfunction even before the first cardiovascular event. This emphasizes the need for further research to better understand the consequence of myocardial infarction further damaging an already injured heart.

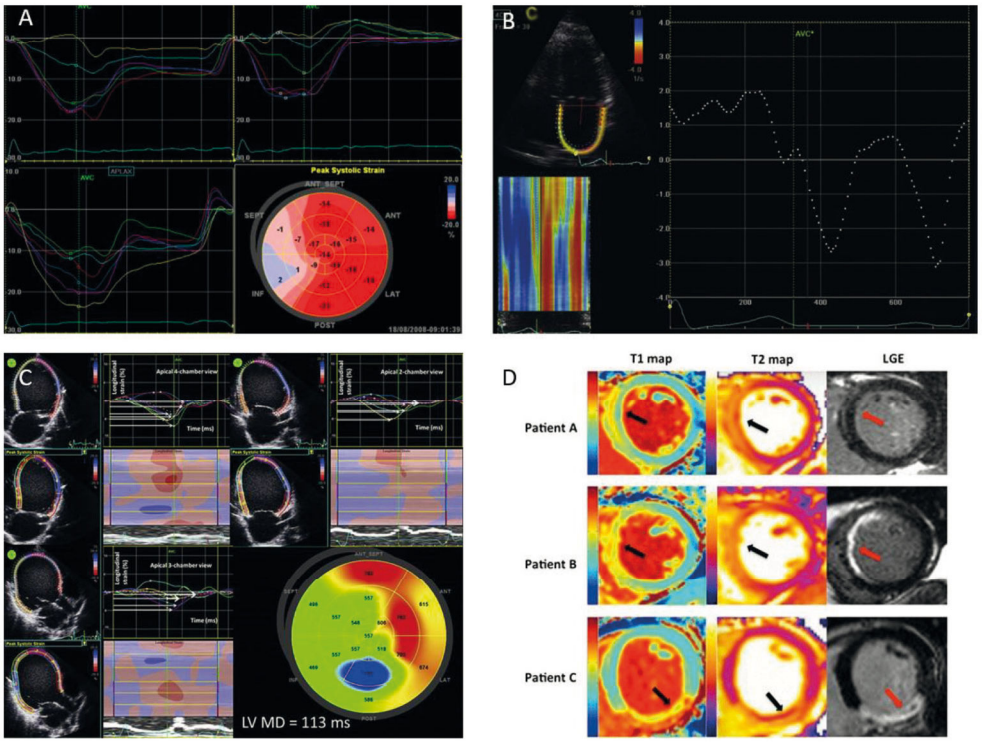
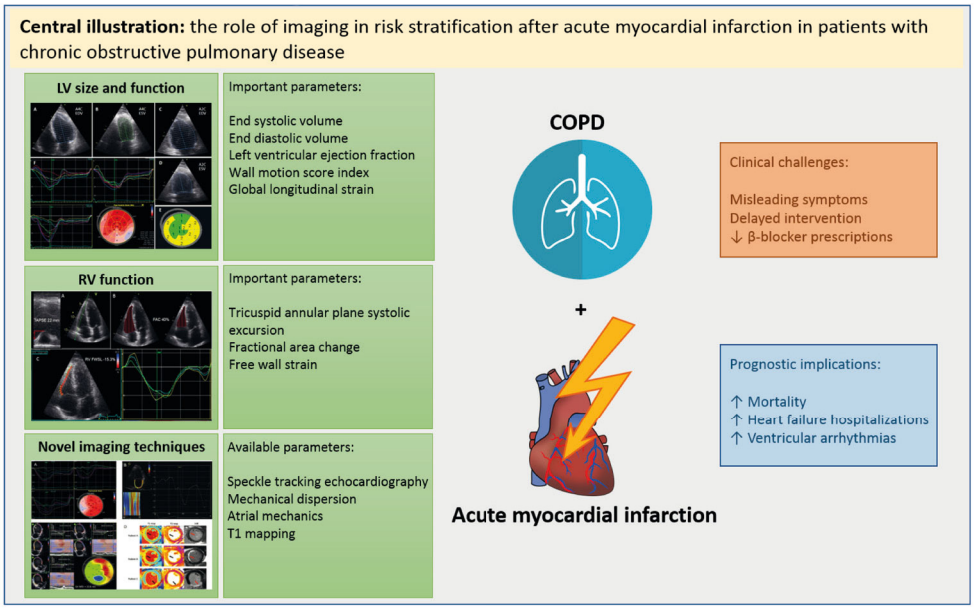


Figure 4. Examples of novel imaging techniques for risk assessment. Reproduced from (A) Delgado et al. [85], (B) Antoni et al. [86], (C) van der Bijl et al.[71] and (D) Bulluck et al. [79].

Conclusion

Patients with COPD carry an increased risk of AMI through various pathophysiological pathways. Following AMI, the rate of adverse events is higher in COPD patients when compared to patients without COPD, which might in part be due to a delay in recognition and subsequent revascularization. Echocardiography has already shown that COPD patients might be more vulnerable for ischemia, leading to worse cardiac function when compared to patients without COPD. Advanced imaging techniques could play a pivotal role in risk stratification after AMI in patients with (and without) COPD.



Outline of the thesis

The first objective of this thesis was to investigate the influence of chronic obstructive pulmonary disease (COPD) on cardiac function as assessed with echocardiography, in patients with acute myocardial infarction or atrial fibrillation. Secondly, this thesis aimed at evaluating the prognostic implications of COPD in patients with cardiac diseases and the role of imaging in risk stratification in this specific patient population.

In **Part 1**, the impact of COPD on left- and right ventricular function after acute myocardial infarction is discussed. **Chapter 2** evaluates the differences in infarct size between patients with- and without COPD admitted with an acute myocardial infarction by using conventional measures such as biomarkers and LV ejection fraction, but also advanced 2-dimensional speckle tracking echocardiography derived LV global longitudinal strain. The prognostic implications of LV global longitudinal strain in patients with acute myocardial infarction and concomitant COPD are thereafter discussed in **Chapter 3**. In

Chapter 4, several echocardiographic parameters for RV dysfunction, i.e tricuspid annular plane systolic excursion, fractional area change, tricuspid annular systolic excursion velocity and free wall strain, were analysed to estimate the presence of RV dysfunction in patients with- and without COPD admitted with acute myocardial infarction as well as the impact on survival.

Part 2 provides an insight in the influence of COPD on the development of atrial arrhythmias. **Chapter 5** investigates the incidence of atrial arrhythmias in the first year after acute myocardial infarction in patients with- and without COPD. The impact of COPD on atrial function, as assessed by speckle tracking echocardiography derived atrial reservoir strain, in patients with atrial fibrillation is discussed in **Chapter 6**.

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