Anemia and erythropoietin in cardiovascular disease
Kleijn, Lennaert
Anemia and its association with hemodynamics in a broad spectrum of cardiovascular patients

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Under revision
Abstract

Background:
Anemia is frequently observed in patients with cardiovascular disease. Multiple factors have been associated with anemia, but the role of hemodynamics is largely unknown. Therefore, we investigated the association between hemoglobin (Hb) levels, hemodynamics and outcome in a broad spectrum of cardiovascular patients.

Methods:
A total of 2009 patients who underwent right heart catheterization at the University Medical Center Groningen, the Netherlands, between 1989 and 2006 were identified and data were extracted from electronic databases. Anemia was defined by the WHO criteria (male: hemoglobin < 13.0 g/dL, female: hemoglobin < 12.0 g/dL). The associations between central venous pressure (CVP), cardiac index (CI), systemic vascular resistance (SVR), hemoglobin (Hb), anemia and all cause mortality were assessed with linear, logistic and Cox-proportional hazards analysis.

Results:
The mean age was 57 ± 15 years, 57% were male, mean Hb was 8.3±0.3 g/dL, and 27.4% of the patients were anemic. Patients with anemia had higher CVP levels (7.0±5.4mmHg) compared to non-anemic patients (5.6±4.1 mmHg; p<0.001). CI was slightly higher in anemic patients; 3.0±2.9 L/min/m² vs. 2.9±0.8 L/min/m² (p<0.001), whereas SVR was significantly lower (1212±479 dyn x sec x cm⁻⁵ vs. 1356±555 dyn x sec x cm⁻⁵, p<0.001). CVP and CI were both independent predictors of anemia (OR 1.49; CI1.24-1.81, p<0.001 and OR: 1.93; CI1.54-2.42, p<0.001, respectively). Hemoglobin and CVP were both independent predictors of survival. Patients with anemia and an elevated CVP had the worst prognosis (HR 2.17; 95%CI 1.62-2.90; p<0.001). The impact of elevated CVP and anemia on prognosis was independent of CI and renal function.

Conclusion
Anemia is common in cardiovascular patients and independently related to an elevated CVP and CI. Patients with both elevated CVP and anemia have the worst prognosis, independent of cardiac index.
Background

Anemia is a comorbidity frequently observed in cardiovascular patients.\(^1\) Its presence is independently associated with morbidity and mortality in a broad range of cardiovascular diseases, including heart failure, myocardial infarction and patients with suspected angina.\(^1\)\(^-\)\(^6\)

The etiology of anemia in cardiovascular patients is mostly studied in heart failure (HF) cohorts. These observations have shown that causes for anemia are multifactorial. Several mechanisms may contribute to lower hemoglobin (Hb) levels\(^7\), such as an inadequate production of erythropoietin (EPO)\(^8\), chronic kidney failure\(^9\), haematinic abnormalities\(^10\), use of medication\(^11\), and bone marrow dysfunction\(^12,13\). Elevated levels of cytokines also play a role in the anemia observed in patients with HF.\(^14\) Although not all of these factors have been studied, similarities exist in the etiology of anemia in patients with other cardiovascular diseases. For instance, in acute coronary syndromes, inflammatory factors may play an import contributing role.\(^15\)

There is only limited data available on the association between hemodynamics and hemoglobin levels. Most data come from experimental studies performed in the 1970s and 1980s. It has been shown that acute isovolumic anemia results in an increased cardiac output (CO) and heart rate (HR), and a reduced systemic vascular resistance (SVR).\(^16\)\(^-\)\(^18\) The few studies appearing on chronic severe anemia show that the increased CO is mostly accomplished by increasing stroke volume.\(^19,20\) However all these studies have been performed in experimental settings and data in human subjects, especially the association with outcome, are lacking. In the current study we investigated the association between hemodynamic parameters, hemoglobin levels and outcome in a broad spectrum of cardiovascular patients with varying etiologies.

Methods

Case identification

Using the patient registration system of the University Medical Center Groningen, The Netherlands, all patients that underwent right heart catheterization between January 1, 1989, and December 31, 2006 were identified. All performed intracardiac measurements were extracted from the patients file. Only unique cases were used. The study was performed following the UMCG research code and approved by the local medical ethical committee.
Data extraction
Retrospective chart review was performed to analyze characteristics of all patients that were identified during the electronic search as previously described. For each patient, date of birth, sex, race, weight and height were collected. Comorbid conditions, including hypertension, coronary artery disease, cardiac valve disease, congenital heart disease, history of stroke, hypercholesterolaemia, and diabetes, in addition to medical treatment at the time of catheterization were extracted. Survival status was determined using the electronic patient registration database of the University Medical Center Groningen. Follow up started at the moment of catheterization. The primary endpoint of interest was all cause mortality.

Heart catheterization
Hemodynamic variables obtained during catheterization included systolic blood pressure (SBP; mm Hg), diastolic blood pressure (DBP; mm Hg), CO (thermodilution, L/min), PCWP (mm Hg) and right atrial pressure as indicator of CVP (CVP, mm Hg). Cardiac index (CI; L/min/m²) was determined as cardiac output divided by the body surface area, which was calculated as: 0.007184·weight⁰.⁴²⁵·length⁰.⁷²⁵. SVR (dyn x sec x cm⁻⁵) was calculated as mean arterial pressure minus CVP times 80, divided by cardiac CO. Measurements obtained from cardiac catheterization were obtained from the patient during a resting state.

Laboratory measurements
Routine laboratory assessments at catheterization were extracted from the electronic registration database. If no lab was available at the day of catheterization, most recent measurements were taken within three months prior to catheterization.

Definitions
Anemia was defined according to the WHO criteria as Hb<13 g/dL for men and Hb<12 g/dL for women. To define elevated CVP, we dichotomized CVP at the highest quartile representing a cut-off value of 8 mm Hg. Furthermore, cardiac dysfunction was defined as a cardiac index below 2.5 L/min/m², as previously described.

Statistical analysis.
Results are presented as mean ± standard deviation (SD) when normally distributed and as median and interquartile range (IQR) when skewed distributed and as numbers and percentages for categorical variables. Differences between groups were compared
with Student’s t-test, χ²-test or Mann-Whitney U testing where appropriate. The relation between CVP and Hb or anemia was assessed with standard linear or logistic regression analysis respectively. The variables age, gender, CVP, CI, eGFR, heart rate, SVR, DBP, SBP, history of DM, history of heart transplant, congenital heart disease as reason for catheterisation, diuretics use, Angiotensin Converting Enzyme (ACE) inhibitors or Angiotensin Receptor Blocker (ARB) use, Mineralocorticoid Receptor Antagonist (MRA) use were assessed for their univariate association with Hb or anemia. Variables that showed a significant (p<0.10) univariate association were manually entered in a stepwise multivariable model based on the strength of their univariate association. A cox regression analysis was performed with interaction analysis of Hb and CVP. Variables that showed a significant association, were manually entered in a stepwise backward multivariable model based on strength of univariate association. Multivariable associated variables were adjusted for all univariable associated variables. In addition interaction between Hb and CVP was assessed in this model.

Kaplan-Meier survival plots were constructed to display the influence of anemia and increased CVP on all cause mortality. The association between anemia, CVP, cardiac dysfunction and all cause mortality was assessed by Cox proportional hazards regression analysis. Univariate hazard ratio (HR) and 95% confidence interval (95%CI) of death from any cause were calculated for CVP, anemia or both. Multivariable Cox regression models were then constructed to study the effect of CVP, SVR, CI and anemia on

Table 1. Indications for right heart catheterization

<table>
<thead>
<tr>
<th>Indication</th>
<th>Percentage of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Failure</td>
<td>18.8</td>
</tr>
<tr>
<td>Aortic Valve Stenosis</td>
<td>16.3</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>13.8</td>
</tr>
<tr>
<td>Mitral Valve Insufficiency</td>
<td>13.4</td>
</tr>
<tr>
<td>Pre Transplantation</td>
<td>12.5</td>
</tr>
<tr>
<td>Rhythm Disorder</td>
<td>5.3</td>
</tr>
<tr>
<td>Aortic Valve Insufficiency</td>
<td>5.3</td>
</tr>
<tr>
<td>Pulmonary Hypertension</td>
<td>3.3</td>
</tr>
<tr>
<td>Post Heart Transplantation</td>
<td>2.4</td>
</tr>
<tr>
<td>Mitral Valve Stenose</td>
<td>1.0</td>
</tr>
<tr>
<td>Pulmonary Valve Insufficiency</td>
<td>0.8</td>
</tr>
<tr>
<td>Pulmonary Valve Stenosis</td>
<td>0.3</td>
</tr>
<tr>
<td>Other</td>
<td>6.8</td>
</tr>
</tbody>
</table>
mortality after adjusting for predictors of mortality in HF (age, gender, eGFR, diuretics use, ACE/ARB use, MRA use, coronary artery disease, diabetes mellitus and reasons for catheterization aortic valve insufficiency, pre-transplantation, heart failure or rhythm disturbances). The assumption of proportional hazards was assessed by graphing the HR according to their category after multivariable interaction analysis. All tests were 2-tailed and a p-value<0.05 was considered statistically significant. All analyses were performed with STATA version 12.0.

Results

Demographics

Between 1989 and 2006, a total of 3757 right heart catheterizations were performed.
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Of these, 2557 (68%) were first or only right heart catheterizations of unique patients. Patients having no hemoglobin levels available (n=549) were excluded. Our final study population contained 2009 subjects. Indications for right heart catheterization are shown in table 1.

Baseline demographics of the patient population according to the presence or absence of anemia are presented in table 2. Mean age was 57 ± 15 years and 43% were female. Anemia was present in 27.4%, an elevated CVP in 20.6% and 31.8% of the patients had evidence of cardiac dysfunction, defined as cardiac index of less than 2.5 L/min/m². Anemic patients had significantly lower systolic and diastolic blood pressures, a

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>beta</td>
<td>P-value</td>
</tr>
<tr>
<td>Age</td>
<td>-0.129</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Gender</td>
<td>0.246</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>eGFR</td>
<td>0.257</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CVP</td>
<td>-0.158</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cardiac Index</td>
<td>-0.137</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>DBP</td>
<td>0.175</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>History of Diabetes</td>
<td>-0.107</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diuretic Use (Yes)</td>
<td>-0.138</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ACEi or ARB use</td>
<td>-0.049</td>
<td>0.039</td>
</tr>
</tbody>
</table>

Table 3. Univariate and multivariable predictors for hemoglobin levels.

SBP = systolic blood pressure; DBP = diastolic blood pressure; CO = cardiac output; CVP= central venous pressure; eGFR = estimated glomerular filtration rate; DM = Diabetes Mellitus ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker. Values are corrected for age and gender.

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lower GFR and more frequently had a history of diabetes. Other comorbidities were comparable between anemic and non-anemic patients. Patients with anemia were more often using diuretics, ACE inhibitors and MRAs compared to non-anemic patients. Heart rate was significantly higher in anemic patients. Anemic patients had a significant higher CVP and CI, whereas SVR was lower. Stroke volume was comparable between anemic and non-anemic patients. Increased CVP was observed in anemic patients and this was most pronounced in patients with a low cardiac index (figure 1).

**Association between hemoglobin, anemia and CVP.**

Table 3 shows the linear regression analysis on univariable and multivariable predictors of hemoglobin levels. Adjusted for age and gender, hemoglobin levels were significantly correlated with eGFR, CVP, CI, diastolic blood pressure, history of DM, diuretic use and ACEi or ARB use. There was no significant correlation between SVR and hemoglobin levels. In multivariable analysis, CVP and CI remained independent predictors of hemoglobin levels.

Table 4 shows the outcomes of a multivariable logistic regression analysis for determinants of anemia. The multivariable regression model showed that CI, eGFR,

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate OR (95% CI)</th>
<th>P-value</th>
<th>Multivariable OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.01 (1.00 – 1.01)</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>0.99 (0.81 – 1.20)</td>
<td>0.91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVP per 5 mmHg</td>
<td>1.36 (1.23 – 1.52)</td>
<td>&lt; 0.001</td>
<td>1.49 (1.24 – 1.81)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CI per l/min/m²</td>
<td>1.28 (1.12 – 1.46)</td>
<td>&lt; 0.001</td>
<td>1.93 (1.54 – 2.42)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>eGFR (per 10 ml/min/1.73 m²)</td>
<td>0.83 (0.79 – 0.86)</td>
<td>&lt; 0.001</td>
<td>0.85 (0.79 – 0.92)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Heart rate (per 10 bpm)</td>
<td>1.13 (1.06 – 1.20)</td>
<td>0.001</td>
<td>1.12 (1.01 – 1.24)</td>
<td>0.03</td>
</tr>
<tr>
<td>SBP (per 10 mmHg)</td>
<td>0.96 (0.92 – 1.00)</td>
<td>0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP (per 10 mmHg)</td>
<td>0.79 (0.72 – 0.86)</td>
<td>&lt; 0.001</td>
<td>0.79 (0.66 – 0.94)</td>
<td>0.009</td>
</tr>
<tr>
<td>Medical History</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>1.79 (1.27 – 2.53)</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reason for Catheterisation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>0.25 (0.09 – 0.71)</td>
<td>0.015</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post HTx</td>
<td>3.94 (2.13 – 7.29)</td>
<td>&lt; 0.001</td>
<td>7.44 (2.08 – 26.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEi or ARB</td>
<td>1.28 (1.04 – 1.59)</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>1.64 (1.33 – 2.03)</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRA</td>
<td>1.73 (1.23 – 2.43)</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SBP = systolic blood pressure; DBP = diastolic blood pressure; CO = cardiac output; CVP= central venous pressure; eGFR = estimated glomerular filtration rate; HTx = heart transplantation; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker. MRA = Mineralocorticoid receptor antagonist. Values are corrected for age and gender.
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Heart rate, diastolic blood pressure and post heart transplantation and CVP were independent predictors of anemia. The relation between CVP and anemia was comparable in patients with a reduced CI and in patients with a normal CI (OR: 1.07 per mm Hg; 95% CI 1.02-1.13; p<0.008 vs. OR: 1.13 per mm Hg; 95% CI 1.11-1.19; p<0.0001). Since eGFR influences hemoglobin levels, we performed interaction analysis to study the influence of CVP, CI and eGFR and the presence of anemia. CVP, and eGFR did not have a significant interaction on the presence of anemia (p=0.370) whereas CI and eGFR did have significant interaction on the presence of anemia (p=0.001). The contribution of CVP on the total hemoglobin variance was more pronounced in patients with lower CI compared to patients with a normal CI (table 7).

### Prognostic value of anemia, CVP and CI

During a median follow up of 7 years, 707 patients (35%) patients died. In multivariable cox regression analysis, Hb was significantly associated with mortality (HR 1.15 per g/dL decrease; 95% CI 1.08-1.23; p<0.001), whereas CVP was not (table 5). When entering interaction terms, CVP and hemoglobin had a significant interaction on prognosis (p=0.011). Therefore, to evaluate whether anemia with increased CVP was associated with an adverse outcome, we divided patients into four groups based on the presence...
or absents of anemia and elevated CVP. (table 6) Kaplan Meier survival curves of the four groups are presented in figure 2. Multivariable interaction analysis revealed that anemia with increased CVP was associated with a higher mortality (HR 2.17; 95% CI 1.62-2.90; p<0.0001) than anemia in patients with a normal CVP (HR 1.52; 95% CI 1.17-1.98; p=0.0002). An elevated CVP was only associated with an impaired outcome in the presence of anemia. Importantly, the increased mortality associated with anemia and CVP was independent of the presence of cardiac dysfunction (figure 3).

**Discussion**

In the present analysis we show the association of anemia with hemodynamics in a broad spectrum of cardiovascular patients. CI, CVP and SVR are all associated with anemia. Furthermore, anemia in the presence of elevated CVP is associated with a worse prognosis than anemia with normal CVP. Importantly, the association between anemia, CVP and prognosis is independent of cardiac index. Only limited data exists on the association with anemia and CVP in patients with cardiovascular disease. As mentioned before, experimental studies have shown that

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariable*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>No anemia, low CVP</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>No anemia, high CVP</td>
<td>1.04 (0.78 – 1.40)</td>
<td>0.16</td>
</tr>
<tr>
<td>Anemia, low CVP</td>
<td>1.26 (1.01 – 1.57)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Anemia, high CVP</td>
<td>2.56 (1.98 – 3.32)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*adjusted for all univariate associated variables
CVP = central venous pressure
anemia lowers blood viscosity, decreasing peripheral vascular resistance and increasing cardia output, sympathetic tone, neurohormonal activation and heart rate. In our study in human subjects we can confirm these findings that SVR is lower in patients with anemia. In acute moments of isovolumic hemodilution the cardiac output can be increased up to 150% of normal in healthy volunteers. Experimental models of chronic severe anemia have shown that the increase in CO is mediated mainly by an increased SV. In our analysis we observed that, anemic patients have indeed higher cardiac output although this is mainly mediated by an increase in HR. We did not observe differences in stroke volume between anemic and non-anemic patients. This might be explained by the fact that our cohort contains cardiovascular patients with myocardial dysfunction due to different etiologies. These patients might not have the functional capacity to increase SV and rely on HR response to adjust cardiac output.

Perhaps the most intriguing finding of our analysis is the interaction between CI, CVP and anemia. Anemia in patients with cardiac dysfunction (defined as a CI < 2.5 L/m²) and increased CVP may be the result from congestion. Anemia itself can cause fluid retention through vasodilation which in turn may lead to neurohormonal activation and water and salt retention. However this mechanism probably only plays an important role in patients with severe anemia (Hb<10 g/dL). Since only 6% of our patients had hemoglobin levels below 10 g/dL, it seems more plausible that congestion itself resulted in anemia instead of the opposite.
In heart failure patients, anemia is commonly observed. In a large meta-analysis we previously showed that one third of the HF patients were anemic.\textsuperscript{2} Studies focusing on the etiology of anemia in these patients found that increased extracellular volume was associated with anemia.\textsuperscript{27,28} For instance in a study by Westenbrink et al, extracellular volume was measured in chronic HF patients using 125I-Iotholamate. Although patients did not have clinical symptoms of HF, the increased extracellular volume was independently associated with hemoglobin levels.\textsuperscript{27,28} Furthermore, much as clinically used jugular vein distention is a poor indicator of extracellular volume or CVP, CVP and extracellular volume are correlated.\textsuperscript{26} In our cohort, an elevated CVP was also observed in anemic patients with a normal CI which may indicate that other etiologies with a preserved CI could play a role, for example heart failure with a preserved ejection fraction, isolated right sided heart failure or non-cardiac etiologies including nephrotic syndrome. The contribution of CVP to the total variance of Hb was less in patients with a preserved cardiac function (i.e. CI ≥ 2.5 L/m\textsuperscript{2}) compared to patients with a low CI. This might suggest that especially in patients with an impaired CI, hemodilution may play a role in the etiology of anemia.

The kidneys play a major role in the etiology of anemia.\textsuperscript{29,30} Through production of erythropoietin they are the main stimuli for erythropoiesis. Our current analysis shows indeed that renal function is an important predictor of anemia. One might speculate that the correlation between hemodynamics and anemia can be explained by hypoperfusion of the kidney related to lower perfusion pressure as a result of elevated CVP and lower CI. Indeed, a significant interaction between CI and renal function could be demonstrated on the presence of anemia. This indicates that kidney hypoperfusion could play a role in the presence of anemia. However, a significant interaction with CVP and renal function on the presence of anemia could not be demonstrated, suggesting

\begin{table}[h]
\centering
\begin{tabular}{lcc|cc}
\hline
Variable & \multicolumn{2}{c|}{Cardiac Index ≤ 2.5} & \multicolumn{2}{c}{Cardiac Index >2.5} \\
& Beta & P-value & Beta & P-value \\
\hline
Age & -0.047 & 0.4072 & -0.014 & 0.7020 \\
Gender & 0.213 & 0.0003 & 0.247 & < 0.0001 \\
eGFR & 0.159 & 0.0058 & 0.235 & < 0.0001 \\
CVP & -0.334 & 0.0001 & -0.069 & 0.0350 \\
\hline
\end{tabular}
\caption{Multivariable regression analysis for hemoglobin stratified by cardiac index.}
\end{table}

eGFR; estimated glomerular filtration rate. CVP; central venous pressure.
that CI is more important for the cardio-renal-anemia axis than CVP.

Regarding survival, CI is an independent predictor of survival in our cohort. We could not demonstrate an independent effect of CVP on outcome in the total cohort. Previously, an elevated CVP has been associated with an impaired outcome, in patients with advanced heart failure, congenital heart disease, lung transplantation and end stage renal failure.\textsuperscript{31-34} However these studies did not take hemoglobin levels into account. We found that CVP is only associated with an increased mortality in the presence of anemia, independent of CI and renal function. This additional risk of death when an elevated CVP exists in conjunction with anemia has not previously been described, but may be explained by the strong prognostic value of hemoglobin on outcome and the correlation between CVP and hemoglobin.

There are several limitations to our study. Due to its retrospective design, the etiology of anemia could not be assessed in detail. Therefore, our study merely indicates that there is an association between hemodynamics, anemia and prognosis and we cannot determine a causal relation. It should also mentioned that CVP has a high inter-individual variability and reflects an intra thoracic measurement that can be influenced by numerous factors other than plasma volume, for instance dietary intake and kidney dysfunction.\textsuperscript{35} Furthermore, our study included patients with congenital heart disease. As a plethora of congenital heart diseases exists, these could also include patients with Eisenmenger syndrome. These would thus bias our results. As the fraction of these patients in our analysis is only marginal (<5%) and our aim was to study anemia in a general cardiovascular population, we included these patients in our analysis.

In conclusion, anemia is common in cardiovascular patients and is associated with an increased CVP and CI. Patients with both elevated CVP and anemia have the worst prognosis, independent of cardiac index and renal function.
Chapter 2

References


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