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STRUCTURAL HEART
2021, VOL. 5, NO. 6, 582–587
https://doi.org/10.1080/24748706.2021.1968089

ORIGINAL RESEARCH

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The Clinical Implications of Body Surface Area as a Poor Proxy for Cardiac Output

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ABSTRACT

Background: Prosthesis-patient mismatch (PPM), routinely used to characterize the degree of hemodynamic obstruction caused by a prosthetic heart valve, is associated with adverse patient outcomes after aortic valve replacement (AVR). In the common definition of PPM, the opening area of the valve is related to the patients' cardiac output, by indexing effective orifice area (EOA) with body surface area (BSA). The aim of this study is to assess the implications of using BSA as a proxy for cardiac output.

Methods: 744 patients with normal LV function underwent echocardiographic assessment after surgical AVR. To validate the use of BSA as a proxy for cardiac output, the relation between these variables was analyzed. The effects of BSA on the classification of PPM (EOAi < 0.85 cm^2/m^2) and the presence of hemodynamic obstruction (mean gradient ≥ 20 mmHg and/or Doppler velocity index < 0.35) were estimated.

Results: There was a weak correlation between BSA and cardiac output (r: 0.29, 95% CI: 0.22;0.35), and cardiac output was not proportional to BSA (Cardiac output = 1.5 x BSA +1.9). As a result, the increased risk of patients with a large BSA to be labelled with PPM (OR: 5.2, 95% CI: 2.5,11 per m^2 BSA), was not reflected by a significantly higher risk of hemodynamic obstruction (OR: 1.5, 95% CI: 0.5,4.9 per m^2 BSA).

Conclusions: The current definition of PPM results in a systematic overestimation of hemodynamic obstruction in patients with a larger BSA, and we recommend cautious use in this subgroup.

Abbreviations: AVR: Aortic valve replacement; BMI: Body mass index; BSA: Body surface area; EOA: Effective orifice area; EOAi: Indexed effective orifice area; LVOT: Left ventricular outflow tract; PERIGON: PERIcardial SurGical AOrtic Valve ReplacemeNt Pivotal Trial; PPM: Prosthesis-patient mismatch; TTE: Transthoracic echocardiography; VARC-2: Valve Academic Research Consortium-2.

ARTICLE HISTORY Received 25 September 2020; Revised 27 July 2021; Accepted 5 August 2021

KEYWORDS Prosthesis-patient mismatch; body surface area; epidemiology; prosthetic valves; AVR

Introduction

Prosthesis-patient mismatch (PPM) occurs when the effective orifice area (EOA) of an artificial valve is inadequate for the recipient's hemodynamic requirements.[1] Many studies have demonstrated that (severe) PPM after surgical as well as after transcatheter aortic valve replacement is associated with adverse patient outcomes.[2–5] An EOA that may be acceptable for a small patient may be unsatisfactory for a larger individual. In the assessment of PPM, the effective orifice area (EOA) is therefore commonly corrected for body surface area (BSA). When the resulting indexed EOA (EOAi) falls below 0.85 cm^2/m^2, the patient is considered to have PPM.[6] The Valve Academic Research Consortium-2 (VARC-2) recommended further adjustment of the definition for PPM to ≤0.70 cm^2/m^2 in patients with body mass index (BMI) ≥30 kg/m^2, another height and weight-based measure.[7]

The calculation of BSA only requires height and weight of the patient, which obviously has practical benefits over the measurement of cardiac output with non-invasive diagnostic procedures. However, the most commonly used formula for BSA, the Dubois formula, is derived from a century-old study with only nine subjects that were encased in molds.[8] While it was initially not intended to function as a proxy for cardiac output, the normalization of hemodynamic parameters with BSA has become widespread since then. The latest EACTS/ESC and AHA/ACC guidelines for the management of valvular disease contain numerous references to standards based on BSA ratios.[9,10] This includes cutoff values for indexed stroke volume, indexed tricuspid annulus diameter, etc.

To quantify the degree of hemodynamic obstruction by indexed EOA, BSA must correlate with cardiac output and requires that cardiac output increases proportionally to BSA. For example, a two-fold increase in BSA should correspond to a two-fold increase in cardiac output. The aim of this study was to validate BSA as a proxy for cardiac output and assess the implications of using BSA to calculate EOAi and PPM.

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Supplemental data for this article can be accessed on the publisher's website

Materials and methods

Study and patients

The PERIcardial SurGical AOrtic Valve ReplacemeNt (PERIGON) Pivotal Trial is a prospective, non-randomized trial designed to evaluate the safety and effectiveness of the Avalus aortic valve bioprosthesis (ClinicalTrials.gov: NCT02088554). The methods and primary objectives were previously published.[11,12] The institutional review board of each center approved the protocol and written informed consent was obtained from all patients. In short, 1115 patients with symptomatic moderate or severe aortic stenosis or severe aortic regurgitation underwent surgical aortic valve replacement (AVR) between 2014 and 2017. To exclude that poor LV function confounded our results, the current analysis was limited to 744 patients with preserved postoperative LV systolic function (left ventricular ejection fraction ≥50%). In addition, exclusion criteria for the PERIGON trial were hypertrophic cardiomyopathy, severe diastolic and systolic LV dysfunction, and greater than mild mitral regurgitation or greater than mild tricuspid regurgitation. In this study, the echocardiographic images of the first transthoracic echocardiography (TTE) 3 to 6 months after discharge were analyzed, all by a single core lab (Cardiovascular Core Laboratories, MedStar Health Research Institute, Hyattsville, USA).

Echocardiographic measurements

EOA was calculated with the continuity equation.[13] Individually measured EOA instead of reference EOA from the literature was used in this study, as the categorization of EOAi for the classification of PPM is supported by the strong exponential relation between mean gradient and measured EOA.[6] Stroke volume was determined at the level of the left ventricular outflow tract (LVOT), by multiplying the velocity-time integral with the cross-sectional area of the LVOT. To obtain cardiac output, stroke volume was multiplied by the heart rate. Mean gradient was calculated with the simplified Bernoulli equation, and Doppler velocity index (DVI) was calculated with the velocity-time integral of the left ventricular outflow tract (LVOT), divided by the velocity-time integral across the aortic prosthesis. In accordance with the VARC-2 criteria, hemodynamic obstruction was defined as having a mean gradient ≥20 mmHg and/or Doppler velocity index <0.35.[7]

EOAi was calculated as the ratio of EOA and BSA. The latter was calculated using the Dubois formula[8] (BSA (m^2) = 0.007184 x Height$^{0.725}$ x Weight$^{0.425}$). Patients were classified as having PPM according to standard criteria, proposed by Pibarot and recommended by the American Society of Echocardiography.[2–4,14] PPM was defined by an EOAi ≤ 0.85 cm^2/m^2, whereby the cutoff point for moderate PPM was 0.66–0.85 cm^2/m^2, and severe PPM was ≤0.65 cm^2/m^2. An additional analysis was performed with the VARC-II criteria, which includes lower thresholds for patients with a BMI ≥ 30 kg/m^2; PPM was defined by an EOAi ≤ 0.70 cm^2/m^2, whereby the cutoff point for moderate PPM was 0.61–0.70 cm^2/m^2, and severe PPM was ≤0.60 cm^2/m^2.

Statistical analysis

Categorical variables are summarized as number and percentage, and continuous variables as mean ± standard deviation. Baseline, procedural, and post-operative information of the analyzed cohort are presented. To validate the use of BSA as an accurate proxy for cardiac output, the Pearson's correlation coefficient between these variables was determined. In addition, a linear regression was performed to verify whether cardiac output was proportional to BSA. A non-zero intercept of the best linear fit would indicate that this assumption is incorrect.

To assess the implications of using EOAi as a measure of hemodynamic obstruction, the impact of BSA on EOAi, on mean gradient, and on Doppler velocity index was compared using a Pearson's correlation coefficient. Univariable logistic regression analysis was used to assess the effect of BSA on the risk of being classified with (severe) PPM and having any true hemodynamic obstruction. To investigate the added value of BMI-adjusted cutoff points for PPM,[7,15] the association between BSA and cardiac output, EOAi, mean gradient and Doppler velocity index was analyzed in patients with obesity (BMI ≥ 30 kg/m^2). All tests were 2-tailed and the limit of statistical significance was $p < 0.05$. Statistical analysis was performed with R (R Core Team (2018). R Foundation for Statistical Computing, Vienna, Austria).

Results

PERIGON trial

Of the 744 patients included in this study, the baseline and procedural characteristics are presented in Table 1. Echocardiographic measurements at 3–6 months after discharge are summarized in Table 2; the mean cardiac output was 4.8 ± 1.1 L/min, mean EOAi was 0.79 ± 0.2 cm^2/m^2 and average mean gradient was 12 ± 4 mmHg. The incidence of PPM and severe PPM was 65% and 22%, respectively, while only 70 patients (9%) had a Doppler velocity index <0.35 and/or a mean gradient ≥20 mmHg.

BSA and cardiac output

Although there was a positive relation between BSA and cardiac output (Figure 1), the increase in cardiac output was not proportional to the increase in BSA (Cardiac output = 1.5 x BSA + 1.9). Because the intercept (1.9, 95% CI: 1.2,2.6) was non-zero, a two-fold increase in BSA did not result in a two-fold increase in cardiac output. In addition, the correlation between BSA and cardiac output was weak (r: 0.29, 95% CI: 0.22,0.35). This implies that only 8% (95% CI: 5,12%) of the total variance in cardiac output (r^2) can be explained by BSA. The relationship between BSA and stroke volume was also not proportional (Supplementary Figure 1)

BSA and hemodynamic parameters

Figure 2 shows a negative association between BSA and EOAi (r = −0.15, 95% CI: −0.22,-0.08). An increase of 1 unit in BSA results in an average change in EOAi of −0.13 cm^2/m^2 (95% CI: −0.19,-0.07). In contrast, there was no significant

Table 1. Baseline characteristics of the patients with good LV function in the PERIGON trial.

	n = 744
Age (years)	70 ± 9
Male	560 (75%)
Body Surface Area (m^2)	1.98 ± 0.2
BMI (kg/m^2)	29 ± 5
STS Risk of Mortality (%)	1.85 ± 1.2
NYHA class III/IV	310 (42%)
Diabetes	196 (26%)
Paroxysmal or Chronic AF	65 (9%)
Hypertension	543 (73%)
Chronic Obstructive Lung Disease	72 (10%)
Left Ventricular Hypertrophy	313 (42%)
Left Ventricular Ejection Fraction (%)	61 ± 8
Stroke Volume (mL)	79 ± 21
Cardiac Output (L/min)	5.2 ± 1.4
Mean Gradient (mmHg)	43 ± 17
Peak Gradient (mmHg)	70 ± 26
AVA (cm^2)	0.89 ± 0.5
AVAi (cm^2/m^2)	0.45 ± 0.3
Doppler Velocity Index	0.26 ± 0.1
Isolated AVR	244 (33%)
ACC Time	79 ± 31
Label Valve Size	23 ± 2
- Size 17	1 (0.1%)
- Size 19	29 (4%)
- Size 21	142 (19%)
- Size 23	274 (37%)
- Size 25	228 (31%)
- Size 27	64 (8%)
- Size 29	6 (1%)

ACC – Aortic cross clamp; AF – Atrial Fibrillation; AVA – Aortic valve area; AVAi – Indexed aortic valve area; BMI – Body mass index; BSA – Body surface area; NYHA – New York Heart Association classification; STS – Society of Thoracic Surgery; Categorical variables are summarized as number and percentage, and continuous variables as mean ± standard deviation

Table 2. Summary of echocardiographic findings at the first post-discharge visit.

	n = 744
Mean gradient (mmHg)	13 ± 5
- Mean gradient ≥ 20 mmHg	46 (6%)
Peak gradient (mmHg)	22 ± 8
Doppler velocity index	0.48 ± 0.1
- Doppler velocity index < 0.35	30 (4%)
Left ventricular ejection fraction (%)	62 ± 6
Stroke volume (mL)	74 ± 17
Cardiac Output (L/min)	4.8 ± 1.1
Effective orifice area (cm^2)	1.5 ± 0.3
Indexed effective orifice area (cm^2/m^2)	0.79 ± 0.2
PPM (≤ 0.85 cm^2/m^2)	487 (65%)
- Moderate PPM (0.66–0.85 cm^2/m^2)	321 (43%)
- Severe PPM (≤ 0.65 cm^2/m^2)	166 (22%)

PPM – Prosthesis-patient mismatch. Categorical variables are summarized as number and percentage, and continuous variables as mean ± standard deviation

correlation between BSA and mean gradient (r = 0.04, 95% CI: −0.03,0.11) or Doppler velocity index (r = 0.06, 95% CI: −0.01,0.14). The probability of being labeled with PPM, severe PPM and the presence of hemodynamic obstruction, based on information about mean gradient and Doppler velocity index, is shown in the left panel of Figure 3. While increasing BSA was associated with an increased risk of being labeled with PPM (OR: 5.18, 95% CI: 2.5,11 per m^2 BSA) and severe PPM (OR: 3.0, 95% CI: 1.3,6.9 per unit BSA), it was not associated with an increase in having hemodynamic obstruction (OR: 1.5, 95% CI: 0.5,4.9 per m^2 BSA).

Impact of obesity

The relation between BSA and cardiac output, EOAi, mean gradient, and Doppler velocity index in obese patients was consistent with the results in non-obese patients (Supplementary Figure 2&3). Crucially, BSA was not proportional to cardiac output in both groups. As a result, the decrease in EOAi for increasing BSA was not associated with a significant worsening of Doppler velocity index and mean gradient. In a separate analysis, patients were classified according to the VARC-II criteria for PPM, which assigns lower cutoff values for obese patients. When using the VARC-II criteria, we did not find an association between BSA and the risk of being labeled with PPM (OR: 1.0, 95% CI: 0.5,2.1 per unit BSA) or severe PPM (OR: 1.4, 95% CI: 0.6,3.6 per unit BSA) in the overall cohort (Supplementary Figure 4). Nevertheless, there remained a divergent pattern between the risk of being labeled with PPM and the risk of having hemodynamic obstruction for both obese and non-obese patients separately (Figure 4).

Discussion

In this study of 744 patients with normal LV function after AVR, we analyzed the implications of using BSA to index EOA. Our results show that BSA is a poor proxy for cardiac output. As a result, the current definition of PPM poorly corresponds to the presence of hemodynamic obstruction, including systematic overestimation of hemodynamic obstruction in patients with a larger BSA. These findings challenge the clinical relevance of the definition of PPM that is commonly used.

Already in 1949, Tanner demonstrated that most of the normal standards based on per-BSA ratios are inherently fallacious, as hemodynamic parameters are often not proportional to BSA.[16] For example, a new standard based on indexed stroke volume caused the overestimation of normal stroke volume in larger subjects and the underestimation of normal stroke volume in smaller subjects. This result was confirmed in the more recent work of de Simone *et al.*, who found a negative relation between cardiac index (cardiac output/BSA) and BSA in 970 normotensive subjects.[17]

Intuitively, patients with larger body sizes need more cardiac output and therefore demand bigger valve sizes. However, to use BSA for the indexation of EOA, requires accurate assumptions about the relation between BSA and cardiac output. First, for BSA to reflect cardiac output, a strong correlation between these variables is needed. In our study, however, we only found a correlation of 0.29 between BSA and cardiac output. This means that 92% of the total observed variance in cardiac output was due to factors other than BSA. Second, when EOA/BSA is used to

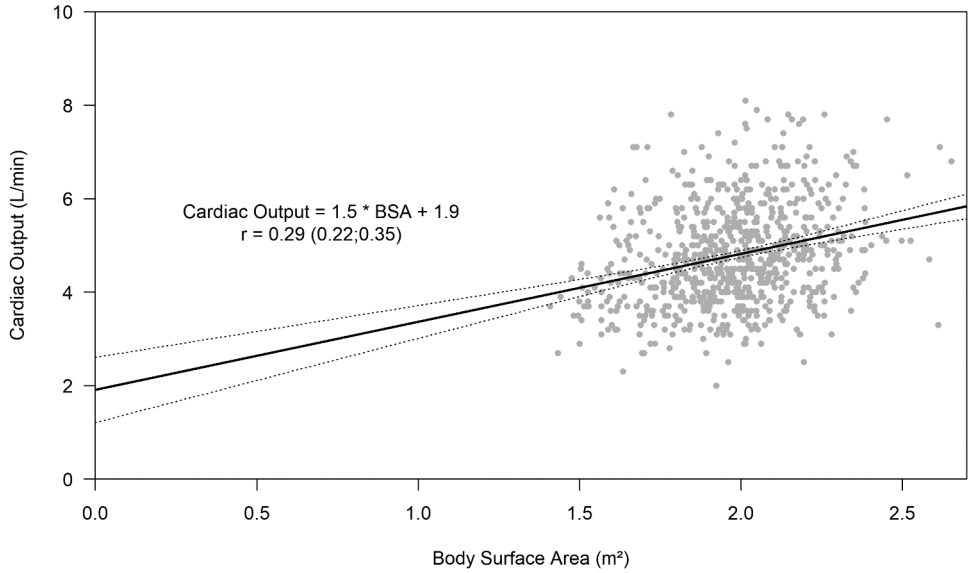

Figure 1. The relationship between BSA and cardiac output.

Linear fit of BSA and cardiac output (black line) with 95% confidence intervals (dashed lines). Of the total variance in cardiac output, only 8% (95% CI: 5;12%) was explained by BSA. In addition, the positive intercept (1.9, 95% CI: 1.2;2.6) indicates that cardiac output was not proportional to BSA; cardiac output and BSA did not increase by the same relative amount.

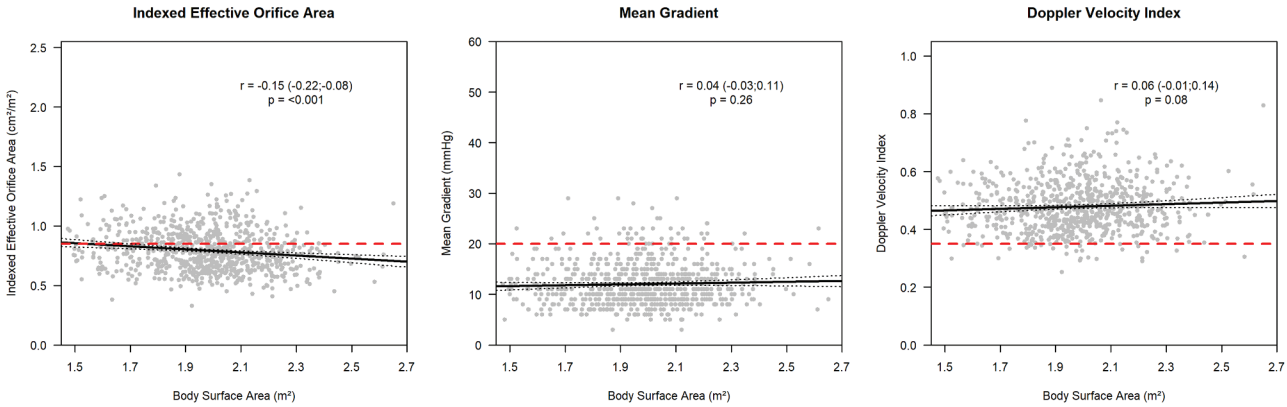

Figure 2. The relationship between BSA and indexed effective orifice area, mean gradient and Doppler velocity index.

For each panel, the linear fit of BSA and the respective hemodynamic parameter (black line) is presented with the 95% confidence intervals (dashed lines). The red line shows the parameter's threshold for obstruction (EOAi ≤ 0.85 cm^2/m^2, mean gradient >20 mmHg and Doppler velocity index <0.35). While there was no significant correlation between BSA and mean gradient or BSA (middle panel) and Doppler velocity index (right panel), indexed effective orifice area decreased by −0.13 cm^2/m^2 (−0.19,-0.07) per 1 m^2 increase in BSA (left panel).

calculate EOAi, it is assumed that cardiac output is proportional to BSA; Cardiac output = k x BSA + 0, with k being a constant. In other words, the ratio of cardiac output/BSA should remain constant for changing BSA (Cardiac output/BSA = k). In Figure 1, it is evident that this assumption does not hold, as the positive intercept indicates a non-proportional relation between BSA and cardiac output (Cardiac output = 1.5 x BSA + 1.9). When BSA is used to index EOA, the cardiac output is overestimated in relatively large patients and underestimated in relatively small patients. This explains why there is a negative correlation between BSA and EOAi, while BSA had no impact on mean gradient or Doppler velocity index. As the current labeling of PPM is based on EOAi thresholds, this ultimately results in a progressive discrepancy between PPM on paper and the presence of hemodynamic obstruction, for increasing BSA.

In studies on the association between severe PPM and mortality, one study showed that severe PPM was only associated with increased mortality in patients with lower BMI, whereas other studies have reported the opposite or no effect.[3] To correct for relatively lower metabolic requirements in obese patients (BMI ≥ 30 kg/m^2), recent guidelines have recommended to use lower EOAi cutoff values for this subgroup.[7] As patients with large BSA are often obese, the use of these BMI-adjusted cutoff values aims to improve the accuracy of PPM to reflect hemodynamic obstruction (Figure 3). The specification of the lower cutoff values for obese patients is not based on any empirical evidence.

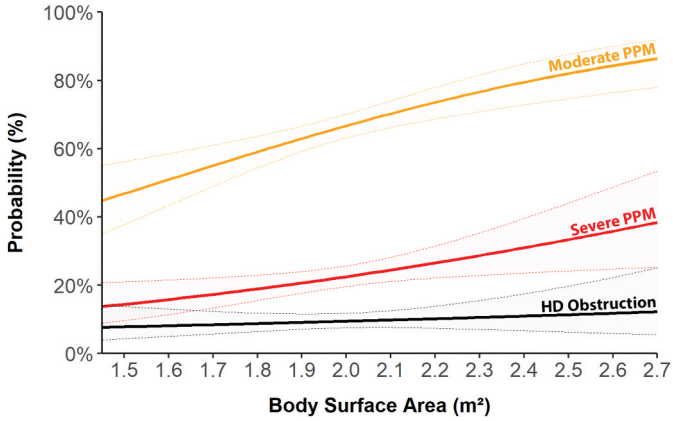

Figure 3. The association between BSA and the probability of having PPM and/or hemodynamic obstruction.

According to the standard criteria, the probability of being classified with PPM (orange line) or severe PPM (red line) increased for larger BSAs, while the risk of hemodynamic obstruction (mean gradient ≥20 mmHg and/or Doppler velocity index <0.35) remained consistent. Minor dashed lines represent 95% confidence intervals.

Moreover, the BMI-adjusted thresholds are still based on the assumption that BSA is proportional to cardiac output within the group of (non-)obese patients, which is questioned by our findings. For both groups, the significant decrease in EOAi for increasing BSA was not associated with a significant worsening of Doppler velocity index and mean gradient (Supplementary Figure 2&3). Therefore, the use of a single EOAi cutoff value for the labeling of PPM still leads to an overestimation of hemodynamic obstruction in patients with larger BSAs, independent of prevalent obesity (Figure 4).

Our main conclusion is that the normalization of effective orifice area with body surface area (BSA), is negatively biased against patients with large BSA, due to the incorrect assumption of a proportional relationship between BSA and cardiac output. It is important to view this finding in the context of our other work on the shortcoming of categorizing indexed EOA cutoff values for the definition of PPM.[18] Together, these studies attenuate the clinical relevance of the current definition of PPM; its definition (EOAi < 0.85 cm^2/m^2) does not reflect an equal degree of hemodynamic obstruction for all patients. In other words, PPM based on EOAi thresholds appears inappropriate to classify patients as having a too small prosthesis.

A search for a better criterion for PPM that is predictive of clinical status should abandon anthropometric measures for the indexation of EOA. While there is a weak association between body size and cardiac output, and therefore the required valve size, cardiac output is also influenced by many other factors (e.g. genetics, lifestyle, etc.). Instead of finding new proxies of normal cardiac output to index EOA, an alternative is to use hemodynamic parameters that are independent of cardiac output for a new definition of PPM, e.g. Doppler velocity index. As calculation of this index does not require BSA and the LVOT diameter,[19] Doppler velocity index is not only easier to calculate than EOAi, but it is potentially also a more reliable measurement of hemodynamic obstruction. Further research needs to focus on Doppler velocity index as a predictor of clinical events related to hemodynamic obstruction after AVR.

Strengths and Limitations

As follow-up in the PERIGON trial was limited, we were unable to study the impact of BSA as a proxy for cardiac output on the use of PPM as a predictor of long-term mortality. Although the discrepancy between PPM and hemodynamic obstruction in subjects with large BSAs suggests that PPM is a less accurate predictor of mortality in these subjects, this requires further validation. An additional limitation is the unknown prevalence of patients with depressed cardiac output but preserved ejection fraction. However, as there is no clear association between BSA

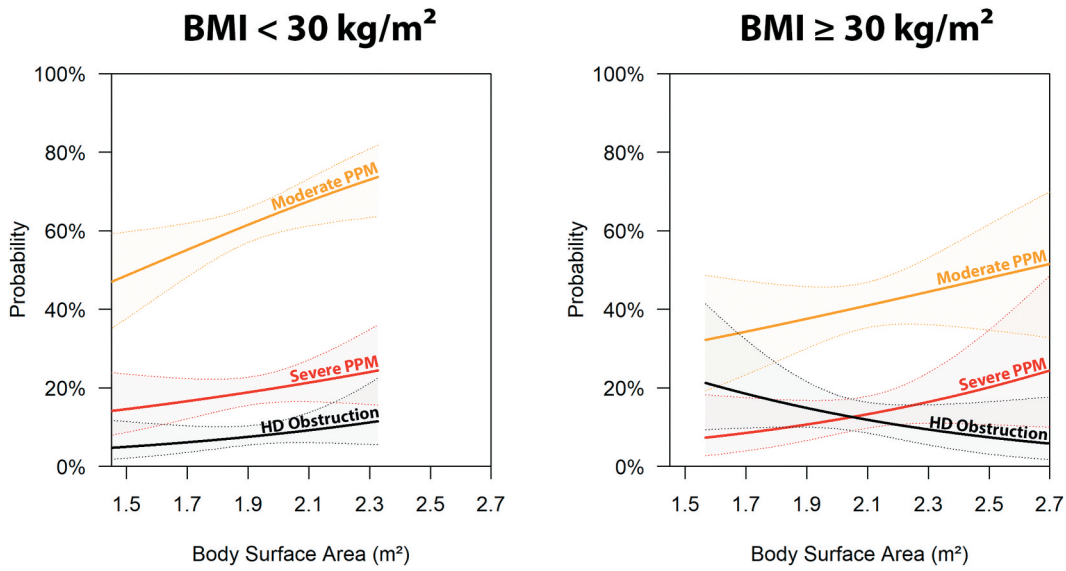

Figure 4. The association between BSA and the probability of having PPM (VARC-II criteria) and/or hemodynamic obstruction in (non-)obese patients.

Despite using the VARC-II criteria, there was a progressive discrepancy between the labeling of (severe) PPM and hemodynamic obstruction for both non-obese (left panel) and obese (right panel) patients, for increasing BSA. Minor dashed lines represent 95% confidence intervals.

and underlying pathology (e.g. infiltrative cardiomyopathy), this condition is an unlikely explanation for the non-proportional relationship between BSA and cardiac output found in our study. An important strength of this study is the use of a core echocardiographic laboratory to assess the hemodynamic parameters in a cohort of patients that received a single type of bioprosthesis. As any residual errors in measurements of hemodynamic parameters are expected to be random, i.e., independent of BSA, the impact of such measurement error on our findings is expected to be negligible.

Conclusion

Utilization of a height and weight-based correction (BSA) for effective orifice area appears incorrect as cardiac output does not increase proportionately to BSA. As a result, the current definition of PPM results in a systematic overestimation of hemodynamic obstruction in patients with larger BSAs, independent of prevalent obesity. Further research needs to focus on a new hemodynamic parameter (e.g. Doppler velocity index) to characterize prosthesis-patient mismatch.

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Funding

PERIGON Pivotal trial is funded by Medtronic.

Disclosure statement

M.D.V. has received a research grant from Medtronic, H.C.H has received institutional research funding from Abbott Vascular, Bayer, Boston Scientific, Edwards Lifesciences, Medtronic, and St. Jude Medical; and has been a consultant for Edwards Lifesciences, Medtronic, and Siemens Healthineers, S.J.H and A.P.K. are employees of Medtronic, R.J.M.K. has received a research grant from Medtronic, consultation and proctoring fees from Medtronic and LivaNova, and participates in speakers bureaus for Medtronic, LivaNova, and Edwards Lifesciences. R.H.H.G., R.A.F.D.L.V.W and P.A.V. have no conflict of interest to declare.

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