Original Article

The impact of heart rate on pulse wave velocity: an in-silico evaluation

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Background: Clinical and experimental evidence regarding the influence of heart rate (HR) on arterial stiffness and its surrogate marker carotid-to-femoral pulse wave velocity (cf-PWV) is conflicting. We aimed to evaluate the effect of HR on cf-PWV measurement under controlled haemodynamic conditions and especially with respect to blood pressure (BP) that is a strong determinant of arterial stiffness.

Method: Fifty-nine simulated cases were created using a previously validated in-silico model. For each case, cf-PWV was measured at five HR values, 60, 70, 80, 90, 100 bpm. With increasing HR, we assessed cf-PWV under two scenarios: with BP free to vary in response to HR increase, and with aortic DBP (aoDBP) fixed to its baseline value at 60 bpm, by modifying total peripheral resistance accordingly. Further, we quantified the importance of arterial compliance (C) on cf-PWV changes caused by increasing HR.

Results: When BP was left free to vary with HR, a significant HR-effect on cf-PWV (0.66 ± 0.24 m/s per 10 bpm, $P < 0.001$) was observed. This effect was reduced to 0.21 ± 0.14 m/s per 10 bpm ($P = 0.048$) when aoDBP was maintained fixed with increasing HR. The HR-effect on the BP-corrected cf-PWV was higher in the case of low $C = 0.8 \pm 0.3$ ml/mmHg (0.26 ± 0.15 m/s per 10 bpm, $P = 0.014$) than the case of higher $C = 1.7 \pm 0.5$ ml/mmHg (0.16 ± 0.07 m/s per 10 bpm, $P = 0.045$).

Conclusion: Our findings demonstrated that relatively small HR changes may only slightly affect the cf-PWV. Nevertheless, in cases wherein HR might vary at a greater extent, a more clinically significant impact on cf-PWV should be considered.

Keywords: 1-D arterial model, aorta, arterial stiffness, blood pressure, haemodynamics

Abbreviations: BP, blood pressure; C, arterial compliance; cf-PWV, carotid-to-femoral pulse wave velocity; HR, heart rate; MAP, mean arterial pressure; PP, pulse pressure

INTRODUCTION

Pulse wave velocity (PWV), defined as the propagation speed of the pulse wave through the circulatory system, constitutes a significant and clinically pertinent index of arterial stiffness [1]. A huge body of clinical evidence, using simple and reproducible noninvasive techniques [2], indicates that arterial stiffness (as assessed via PWV measurement) is a strong, independent predictor of cardiovascular morbidity and mortality in several populations [1,3–5]. Measurement of carotid-to-femoral PWV (cf-PWV) is considered as the gold-standard noninvasive method for the assessment of aortic stiffness [6], and can be readily performed by several noninvasive techniques and devices.

An increased variation in sequential cf-PWV measurements may be often observed [7], due to inherent physiological vascular and haemodynamic variations or/and measurement errors. A parameter that has been questioned for affecting cf-PWV is the heart rate (HR). Cross-sectional population studies have demonstrated either no significant correlation [8] or a positive correlation between cf-PWV and resting HR [9,10]. Albaladejo *et al*. [8] reported that there is no significant rise in cf-PWV when HR is increased. On the contrary, Lantelme *et al*. [10] demonstrated that HR is an important factor of the intrapatient cf-PWV changes in the elderly. Nevertheless, those studies have investigated the potential effect of HR on cf-PWV without isolating the effect of the concurrent increase in blood pressure (BP) with increasing HR. In addition, results from existing acute experimental studies have been also inconclusive [10]. Therefore, it is of utmost importance to investigate more thoroughly the BP-independent cf-PWV-HR relation; especially, now, that the clinical use of cf-PWV is increasing [11–13]. The main objective of the present study was to evaluate and quantify the influence of HR on cf-PWV measurement, and determine potential haemodynamic conditions that modulate the HR- cf-PWV association. Furthermore, we aimed to quantify the potential impact of arterial compliance on cf-PWV changes caused by increasing HR.

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MATERIALS AND METHODS

We used a dataset of virtual individuals with a variety of cardiovascular characteristics. Specifically, 59 virtual individuals were created using a generic 1-D model of the human cardiovascular system [14]. For every individual, the HR was increased at five levels, that is, 60, 70, 80, 90, 100 bpm and PWV was determined at each of them. BP at the ascending aorta and brachial artery was also determined at each HR level. Finally, we calculated the stroke volume (SV) and the mean aortic flow (cardiac output).

We performed two experiment series: with BP free to vary when HR was increased, and with BP fixed to its baseline value (at 60 bpm). For this purpose, the aortic DBP (aoDBP) was maintained constant by altering the total peripheral resistance (TPR). Adjusting TPR compensated for the HR-related changes in cardiac output and allowed us to maintain the pressure level constant. This was done to ensure that potential changes in cf-PWV were the result of the change in HR alone and not due to the expected BP increase.

Generation of the in-silico population

We simulated 59 haemodynamic cases by running an in-silico model of the cardiovasculature using arbitrary sets of input parameters. The values' ranges of the input parameters were selected based on physiological data published in the literature (Table 1) [15–23]. The model that was adopted in the present study has been previously described and validated against in-vivo measurements [14,24].

It comprises the main arteries of the systemic circulation, including a network of the cerebral circulation and the coronary circulation. The governing equations of the model are acquired by integration of the longitudinal momentum and continuity equations over the arterial cross-section. Flow and pressure waves are obtained at an arterial segment-level by solving the governing equations using an implicit finite-difference scheme. Concretely, the simulated flow and pressure waveforms are provided in the form of a vector with respect to the time duration of the cardiac cycle. The arteries are considered as long tapered tubes, and their compliance is defined as a nonlinear function of pressure and location [15]. Nonlinearity and more importantly for the purpose of this study viscoelasticity of the arterial wall is considered following Holenstein *et al.* [25]. Distal vessels are terminated with three-element Windkessel models to consider the resistance of the peripheral vasculature. Contractility of the left ventricle (LV) is simulated with a time-varying elastance model [26,27]. HR is prescribed as an input parameter to the LV model. It should be noted that the model also captures the variation of the ratio of systolic and diastolic duration in the presence of HR changes. Namely, an increase in HR will result to an increase in the systole/diastole duration ratio [28]. The dead volume (V_d) and the time of maximal elastance were kept unchanged and equal to the average values of $V_d = 15.00$ ml and $t_{max} = 340.00$ ms as reported previously [14,29]. Arterial geometry was changed by adapting the height of the arterial tree, as well as the diameter of the arterial segments in order to simulate different body types. The cardiovascular parameters of the entire virtual study population are reported in Table 1.

Data analysis

The values of HR varied between 60 and 100 bpm for each of the virtual cases. At an individual-level at each HR level, cf-PWV, BP (aortic and brachial), SV and mean aortic blood flow were computed. The 'measurements' were performed for both scenarios, namely free-varying pressure and fixed aortic BP.

The cf-PWV was calculated by a foot-to-foot algorithm using the tangential method [30]. Pulse transit time was computed between the carotid artery and the femoral artery. The method uses the intersection point of two tangents on the arterial pressure wave, that is the tangent passing through the systolic upstroke and the horizontal line passing through the minimum of the pressure wave as previously described [30]. The travel length was determined by summation of the lengths of the arterial segments within the transmission path, that is the relevant carotid-to-femoral path. Then, the value of cf-PWV was calculated by dividing the total travel length by the pulse transit time.

In addition, aortic SBP, DBP, mean arterial pressure (MAP) and pulse pressure (PP) were derived from the pressure waveform at the aortic root. Brachial SBP, DBP, MAP and PP were obtained by computing the pressure at the left brachial artery. SV was calculated from the area under the curve of the aortic flow waveform. Mean aortic flow was derived from the mean value of the flow waveform at the aortic root.

TABLE 1. Cardiovascular parameters of the total virtual study population ($n = 59$)

Parameter	Value ($n = 59$)				Ref.
	Min	Max	Mean	SD	
Height (cm)	150.00	200.00	170.00	13.50	
E_{es} (mmHg/ml)	1.14	3.48	2.24	0.60	Chen *et al.* [16], Pak *et al.* [17]
E_{ed} (mmHg/ml)	0.05	0.19	0.11	0.03	Feldman *et al.* [18]
P_{venous} (mmHg)	9.46	22.57	16.17	3.29	Senzaki *et al.* [19]
Aortic diameter (cm)	1.91	3.98	2.74	1.44	Wolak *et al.* [20], Devereux *et al.* [21]
[a]Aortic distensibility ($\times 10^{-3}$/mmHg)	1.00	8.05	4.53	1.90	Segers *et al.* [22],
[a]Brachial distensibility ($\times 10^{-3}$/mmHg)	0.40	3.23	1.82	0.76	Langewouters *et al.* [15]
TPR (mmHg.s/ml)	0.62	1.55	1.13	0.24	Lu and Mukkamala [23]

E_{ed}, end-diastolic elastance; E_{es}, end-systolic elastance; P_{venous}, venous pressure; SD, standard deviation; TPR, total peripheral resistance.
[a]The arterial wall distensibility and the respective lumen radius correspond to a reference transmural pressure of 100 mmHg.

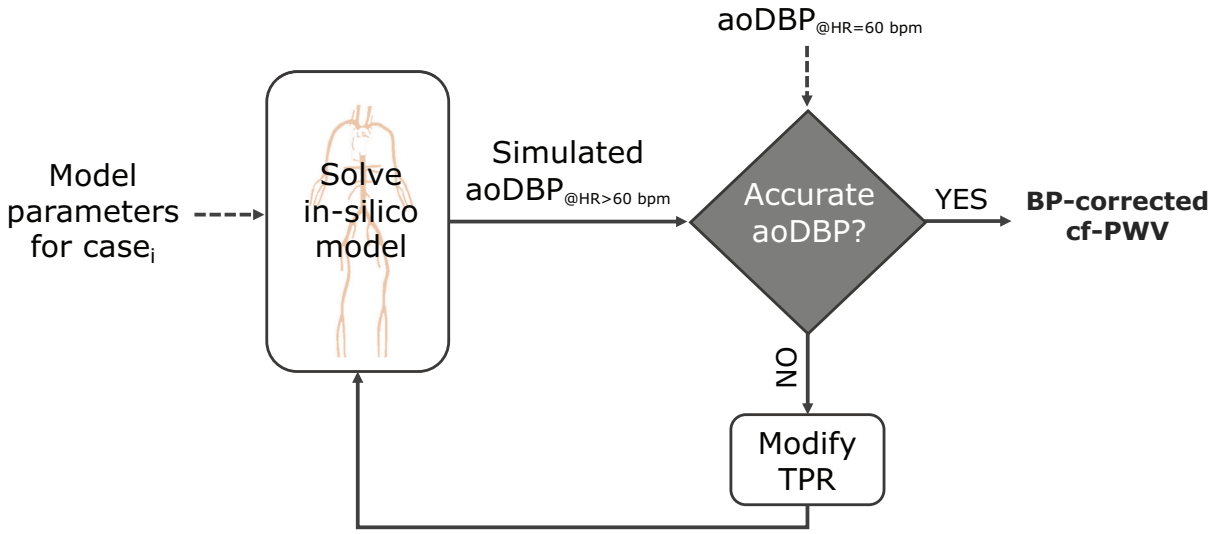

FIGURE 1 Schematic representation of the optimization algorithm that corrects blood pressure. aoDBP, aortic DBP; BP, blood pressure; cf-PWV, carotid-to-femoral pulse wave velocity; TPR, total peripheral resistance.

Blood pressure correction method

To isolate the direct HR effect on PWV from any consequent BP influence, we employed a method to correct for BP; namely, to maintain constant the aortic DBP (aoDBP). The aoDBP was chosen instead of MAP, as cf-PWV was computed using the foot-to-foot method and thus, using the diastolic points of the pulse wave (this point is further elaborated in the Discussion). In this respect, the individual-specific TPR was adjusted. This was achieved by multiplying the TPR with a scaling factor. A gradient-based optimization algorithm was employed to derive the adjusted TPR. With increasing HR (from 60 to 100 bpm) in every individual, the optimization algorithm estimated the optimal TPR that would allow aoDBP to remain constant (equal to its baseline value at 60 bpm) eliminating the expected rise in pressure. The tolerated error for capturing aoDBP was set to 0.01%. Figure 1 provides the schematic representation of the optimization process used to correct cf-PWV measurement for BP changes. Once the algorithm provided the corrected TPR, the 1-D model ran and produced the flow and pressure waves for every segment of the arterial tree. From the solution, we were able to obtain the quantities of interest, including the corrected cf-PWV.

Compliance-dependency of pulse wave velocity response to increasing heart rate

Further investigation was performed to quantify the importance of arterial compliance on the cf-PWV changes caused by increasing HR. The effect of HR on cf-PWV was assessed for two different levels of arterial stiffness. In this respect, the entire sample was divided into two groups based on the total arterial compliance (C) to represent two different levels of arterial stiffness, that is a more elastic tree ($C > 2.00$ ml/mmHg) and a stiffer tree ($C < 2.00$ ml/mmHg). The haemodynamical parameters of the two groups at baseline conditions, that is 60 bpm, are presented in Table 2. With increasing HR, the variable characteristics of the two groups were assessed and compared.

Statistical analysis

The statistical analysis was performed in Python (Python Software Foundation, Python Language Reference, version 3.6.8; http://www.python.org). One-way analysis of variance (ANOVA) for repeated measures was used to determine the effect of HR levels on cf-PWV, SBP, DBP, MAP, SV and cardiac output (CO). Values were reported as mean ± SD. Statistically significant difference was set at the level of P value less than 0.05.

RESULTS

The changes of the measured haemodynamical parameters of the entire population at the five HR values are reported in Table 3.

Under free-varying pressure conditions, a gradual rise in cf-PWV with respect to the HR increase was observed (Fig. 2a, solid line). The values of cf-PWV were reported to be equal to 9.54 ± 1.60, 10.20 ± 1.69, 10.83 ± 1.84,

TABLE 2. Haemodynamical parameters of the two groups with different levels of compliance at baseline (HR = 60 bpm)

Variable$_{@60bpm}$	Low arterial stiffness C = 1.7 ± 0.5 ml/mmHg ($n1 = 28$)	High arterial stiffness C = 0.8 ± 0.3 ml/mmHg ($n2 = 31$)
cf-PWV (m/s)	8.28 ± 0.78	10.67 ± 1.27
Aortic SBP (mmHg)	116.12 ± 24.24	138.05 ± 29.92
Aortic DBP (mmHg)	79.66 ± 14.61	74.69 ± 20.73
Aortic PP (mmHg)	36.45 ± 14.95	63.36 ± 20.56
MAP (mmHg)	91.81 ± 16.98	95.81 ± 22.16
Brachial SBP (mmHg)	129.67 ± 26.61	152.28 ± 28.21
Brachial DBP (mmHg)	76.85 ± 14.42	72.07 ± 20.1
Brachial PP (mmHg)	52.82 ± 19.49	80.22 ± 19.35
Aorto-brachial PP amplification	1.47 ± 0.08	1.3 ± 0.13
Mean aortic flow (l/min)	5.29 ± 1.72	5.05 ± 1.2
Stroke volume (ml)	87.09 ± 28.36	83.13 ± 19.73

C, arterial compliance; cf-PWV, carotid-to-femoral pulse wave velocity; MAP, mean arterial pressure; PP, pulse pressure.

TABLE 3. Haemodynamical characteristics of the entire population with increasing heart rate (from 60 to 100 bpm)

Variable (with no correction for BP)	Value ($n = 59$) mean ± SD					P
	HR = 60 bpm	HR = 70 bpm	HR = 80 bpm	HR = 90 bpm	HR = 100 bpm	
[a]cf-PWV (m/s)	9.54 ± 1.6	10.2 ± 1.69	10.83 ± 1.84	11.5 ± 1.96	12.17 ± 2.07	< 0.001
Aortic SBP (mmHg)	127.64 ± 29.3	133.93 ± 29.89	139.85 ± 30.11	145.87 ± 30.46	151.54 ± 30.89	< 0.001
Aortic DBP (mmHg)	77.05 ± 18.11	86.35 ± 20.12	95.2 ± 21.99	104.31 ± 23.93	113.23 ± 25.92	< 0.001
Aortic PP (mmHg)	50.59 ± 22.5	47.57 ± 21.74	44.64 ± 20.82	41.56 ± 20.09	38.31 ± 19.53	0.015
MAP (mmHg)	93.91 ± 19.8	102.21 ± 21.51	110.08 ± 22.98	118.17 ± 24.52	126 ± 26.1	< 0.001
Brachial SBP (mmHg)	141.55 ± 29.51	148.14 ± 30.16	153.74 ± 30.46	159.61 ± 30.88	165.26 ± 31.42	< 0.001
Brachial DBP (mmHg)	74.34 ± 17.65	83.06 ± 19.6	91.66 ± 21.4	100.53 ± 23.25	109.15 ± 25.18	< 0.001
Brachial PP (mmHg)	67.21 ± 23.69	65.07 ± 22.52	62.08 ± 21.49	59.08 ± 20.57	56.11 ± 19.76	0.041
Aorto-brachial PP amplification	1.38 ± 0.14	1.44 ± 0.16	1.47 ± 0.18	1.51 ± 0.21	1.58 ± 0.28	< 0.001
Mean aortic flow (l/min)	5.17 ± 1.46	5.68 ± 1.64	6.11 ± 1.79	6.44 ± 1.9	6.68 ± 2.01	< 0.001
Stroke volume (ml)	85.01 ± 24.08	80.07 ± 23.16	75.33 ± 22.03	70.86 ± 20.95	66.16 ± 19.92	< 0.001

cf-PWV, carotid-to-femoral pulse wave velocity; MAP, mean arterial pressure; PP, pulse pressure; SD, standard deviation.
[a]The cf-PWV was calculated from the free-varying pressure experiment.

11.50 ± 1.96 and 12.17 ± 2.07 m/s at 60, 70, 80, 90 and 100 bpm, respectively. The difference between cf-$PWV_{@60bpm}$ and cf-$PWV_{@100bpm}$ was 2.64 ± 0.70 m/s (27.73 ± 6.26% with respect to the baseline cf-$PWV_{@60bpm}$). When correction for aoDBP was performed, the cf-$PWV_{BP\text{-}corrected}$ increase was reduced to 9.54 ± 1.60, 9.66 ± 1.60, 9.92 ± 1.69, 10.14 ± 1.75 and 10.37 ± 1.81 m/s ($P = 0.048$) at 60, 70, 80, 90 and 100 bpm, respectively (Fig. 2a, dashed line). The respective differences between the BP-corrected cf-$PWV_{@60bpm}$ and the corrected cf-$PWV_{@100bpm}$ was 0.84 ± 0.36 m/s (8.71 ± 3.12% with respect to the baseline cf-$PWV_{@60bpm}$).

The concomitant HR-related changes on MAP were reported as 93.91 ± 19.80, 102.21 ± 21.51, 110.08 ± 22.98, 118.17 ± 24.52 and 126.00 ± 26.10 mmHg for the five HR values (from 60 to 100 bpm), respectively. A significant effect of HR changes on MAP was observed, with a total average increase in MAP equal to 32.09 ± 7.73 mmHg ($P < 0.001$) for a total increase in HR by 40 bpm. Aortic SBP and DBP were increased with the increase in HR from 60 to 100 bpm by 23.90 ± 7.40 mmHg ($P < 0.001$) and 36.18 ± 9.13 ($P < 0.001$) mmHg, respectively. The increase in aoDBP was markedly higher resulting to a decrease in aortic PP [by 12.28 ± 7.93 mmHg ($P = 0.015$)]. Similar response was observed in the brachial BP with a less significant effect on the PP decrease (by 11.11 ± 6.64 mmHg, $P = 0.041$). Consequently, PP amplification from the aorta to the brachial artery was increased by 14.15 ± 13.67% ($P < 0.001$) for the 40-bpm increase in HR. Finally, SV was decreased by 18.85 ± 5.78 ml ($P < 0.001$), whereas mean aortic flow was increased by 1.52 ± 0.63 l/min ($P < 0.001$) due to the 40-bpm total increase in HR.

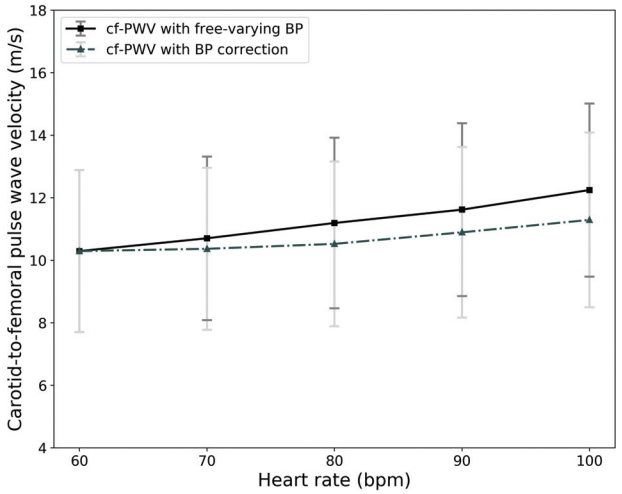

FIGURE 2 Changes in the carotid-to-femoral pulse wave velocity with increasing heart rate under two scenarios: (1) with free-varying blood pressure (BP) (solid line) and (2) with fixed DBP (dashed line).

Influence of arterial stiffness on the heart rate induced changes in carotid-to-femoral pulse wave velocity and blood pressure

Table 4 summarizes the total net change between the maximal HR (100 bpm) and the baseline HR (60 bpm) in every variable for the two groups of arterial stiffness.

TABLE 4. Relative changes in haemodynamical variables at 100 bpm with respect to their baseline values at 60 bpm for the two groups with different levels of arterial compliance

Variable	Low arterial stiffness C = 1.7 ± 0.5 ml/mmHg ($n1 = 28$)	High arterial stiffness C = 0.8 ± 0.3 ml/mmHg ($n2 = 31$)
[a]δ(cf-PWV) (m/s)	2.32 ± 0.53	2.92 ± 0.72
[b]δ(cf-$PWV^{corrected}$) (m/s)	0.64 ± 0.19	1.02 ± 0.38
δ(aoSBP) (mmHg)	26.51 ± 6.45	21.54 ± 7.5
δ(aoDBP (mmHg)	36.21 ± 8.76	36.16 ± 9.59
δ(aoPP) (mmHg)	−9.7 ± 4.78	−14.61 ± 9.44
δ(MAP) (mmHg)	32.97 ± 7.74	31.28 ± 7.77
δ(brSBP) (mmHg)	26.62 ± 6.27	21.09 ± 8.04
δ(brDBP) (mmHg)	35.69 ± 8.37	34.03 ± 9.21
δ(brPP) (mmHg)	−9.07 ± 6.07	−12.95 ± 6.69
δ(ao-$brPP_{ampl}$)	0.26 ± 0.25	0.14 ± 0.13
δ(CO) (l/min)	1.63 ± 0.78	1.42 ± 0.45
δ(SV) (ml)	−18.62 ± 4.66	−19.07 ± 6.71

ao-$brPP_{ampl}$, aorto-brachial PP amplification; aoDBP, aortic DBP; aoPP, aortic pulse pressure; aoSBP, aortic SBP; BP, blood pressure; brDBP, brachial DBP; brSBP, brachial SBP; cf-PWV, carotid-to-femoral pulse wave velocity; *CO*, cardiac output; MAP, mean arterial pressure; SV, stroke volume.
[a]For free-varying blood pressure.
[b]For fixed aortic DBP.

For the group with higher values of arterial compliance, the effect of HR on cf-PWV was found to be equal to 0.58 ± 0.18 m/s per 10 bpm ($P < 0.001$) and 0.16 ± 0.07 m/s per 10 bpm ($P = 0.045$), under the free-varying pressure scenario and the fixed aoDBP scenario, respectively. When the group with stiffer arterial system was assessed, the corresponding quantified effects were reported to be 0.73 ± 0.25 m/s per 10 bpm ($P < 0.001$) and 0.26 ± 0.15 m/s per 10 bpm ($P = 0.014$) for the free-varying pressure and the fixed DBP scenarios, respectively.

It appeared that the increase in HR had a greater effect on PP at the lower than higher arterial compliance level (Table 4). Concretely, a 10-bpm increase in HR resulted to a decrease in PP by 2.42 ± 1.22 mmHg ($P = 0.077$) at $C = 1.7 \pm 0.5$ ml/mmHg (group with low arterial stiffness). The same HR increase led to a PP reduction equal to 3.65 ± 2.39 mmHg ($P = 0.034$) at $C = 0.8 \pm 0.3$ ml/mmHg (group with high arterial stiffness). Similar response was reported for the brachial PP (Table 4). SV was reduced at a slightly greater extend at the low compliance group in comparison to the higher compliance group; this had as a result that CO experienced a smaller increase in the case of high than the case of low arterial stiffness.

DISCUSSION

The present study evaluated the influence of HR on cf-PWV on 59 in-silico individuals. We leveraged the simulation capacity of a previously validated mathematical model of the cardiovasculature in order to create a complete haemodynamical database accessing information that is not easily obtained in a real clinical setting. Mathematical modelling allowed for isolating the inherent HR effect independent of any HR-induced systemic variations, that is BP changes. It was demonstrated that a 10-bpm increase in HR imposes a minimal direct effect on cf-PWV in the total sample. However, in cases of higher HR increase, the accumulative effect may lead to a clinically significant change in cf-PWV measurements. These HR effects on cf-PWV were amplified in cases with increased arterial stiffness.

Despite previous works that investigated the effect of HR on cf-PWV, the inherent mechanisms that are responsible for the variation in arterial stiffness with HR are yet to be elucidated. A possible explanation for the alteration in the arterial stiffness with HR has been related mostly to the concomitant changes in BP with increasing HR and in a lesser degree to the viscoelastic properties of the arterial walls. Previous studies have suggested that it is the HR-induced rise in BP that incites cf-PWV to increase, rather than a direct influence from the HR *per se* [8,31]. Here, we achieved to isolate the BP-dependency on the cf-PWV changes by employing a correction technique that maintained aoDBP constant (while HR increased). The rationale for choosing the aoDBP to be controlled is due to the fact that measurement of cf-PWV using the foot-to-foot method is associated with the vicinity of the diastolic foot, and thus aoDBP. This choice is further supported both theoretically and empirically by previous studies [32–34].

On the basis of our findings, the HR effect on cf-PWV was reported to be equal to 0.66 ± 0.24 m/s per 10 bpm in the presence of BP-free response. When the BP correction method was employed to derive the corrected cf-PWV, the respective effect was reported to be 0.21 ± 0.14 m/s per 10 bpm. This effect was found to be in accordance with previously published data from the work of Tan *et al.* [35], wherein they also reported an effect equal to approximately 0.20 m/s per 10 bpm ($P < 0.001$). We also performed our analysis by keeping the aortic SBP (aoSBP) constant. In this case, the effect of HR on cf-PWV was equal to 0.40 m/s per 10 bpm instead of 0.21 m/s per 10 bpm when the aoDBP was maintained constant. This is rather expected if we consider that the increase in aoSBP is smaller than the increase in aoDBP with increased HR, and, as a result, the BP correction is greater when we choose to maintain fixed aoDBP.

Increased HR was associated with increased MAP and decreased aortic and peripheral PP (brachial PP), as expected. The decrease in central PP was found to be greater in magnitude than the decrease in brachial PP, and thus, an increase in PP amplification was observed. These observations have also been acknowledged in previous studies [8]. It was also noted that the increase in DBP, especially, lead to the PP reduction. Nevertheless, in our data, the increase of PP amplification was less prominent (approximately 14%, $P < 0.001$). According to Pichler *et al.* [36], PP amplification is related to BP level; the higher the BP, the lower the BP amplification. In our study, BP was relatively higher than other published data [8,37] in which a higher increase in PP amplification was observed. Moreover, increasing HR led to a decrease in SV, which was rather expected considering that SV is a major determinant of PP. In contrast, CO was increased due to the large increases in HR.

The correction methodology that was employed in the current study interferes with the TPR, which is the main systemic determinant of aoDBP [38]. An increase in TPR leads to an increase in BP level, and thus to increased arterial stiffness based on the nonlinear pressure-compliance relationship. By employing a correction technique, it is exactly this BP increase that we wish to control. In practice, by decreasing BP, we expect that TPR will also decrease, and vice versa. In our in-silico model, the modification of TPR allows us to achieve the control of BP *per se*. Importantly, a prominent element of our approach is that our manoeuvre is not applied directly to the aorta. On the contrary, we only modify locally the peripheral sites (resistances) without imposing any intervention on the properties of the global arterial tree. Possible interference due to the influence of TPR on cf-PWV (using the foot-to-foot method) has been evaluated by previous studies demonstrating low correlations between the two quantities [39,40].

It should be noted that, although our study population presented a concurrent increase in BP with increased HR, this observation is not systematic in the literature. In studies wherein HR was changed acutely through pacing, despite the fact that some scientists reported a rise in cf-PWV in the presence of a significant parallel increase in BP [9,10], others observed no BP rise with increased HR [8,41–43]. This existing inconsistency makes it hard to determine whether HR, additionally, contributed to the increase in cf-PWV independently of BP. Our objective was to precisely quantify the part of cf-PWV increase that is caused

intrinsically due to the HR changes, and to isolate the cf-PWV increase due to the BP increase. Thus, we simulated and compared the two different phenotypes, namely, where BP was deliberately allowed to vary in response to HR changes that physiologically occur in some individuals, and where BP was controlled so that it remains unchanged when HR varies, which is also apparent in some humans.

It is undeniable that the effect of HR on cf-PWV measurement has been a subject of high controversy. In a previous study, Albaladejo *et al.* [8] have showed that increased HR (introduced acutely by pacing) leads to a rise in cf-PWV accompanied with an increase in BP. The authors also reported an increase in PP amplification that was not, however, associated with a change in aortic stiffness. The cf-PWV change was rather attributed to the interaction between reduced SV and modified wave reflection sites. Nevertheless, their study includes only 11 individuals, whereas the cf-PWV was evaluated under only three averaged levels (low, medium, high), which were not predetermined.

On the contrary, Lantelme *et al.* [10] have claimed that HR changes exert a significant effect on cf-PWV measurement in an elderly population ($n = 22$) in the absence of BP changes. However, concerns have been raised [44] against the Complior technique [45], which was employed to measure cf-PWV in this study. It is likely that increasing HR can affect the shape of the pressure waveform. The sensitivity of the cf-PWV estimation method (Complior apparatus) on the waveform characteristics may explain the discrepancies between their findings and other clinical investigations, as already suggested by Hayward *et al.* [44]. These discrepancies do not allow us to derive a clear understanding on the HR impact on arterial stiffness measurement. Furthermore, evidence from the aforementioned studies was based on cross-sectional population data in which the intrinsic effect of HR on cf-PWV cannot be isolated.

Of particular interest is the study by Tan *et al.* [35] in which the HR effect on cf-PWV was evaluated by isolating the corresponding influence of BP. The cf-PWV measurement was corrected for BP using three methods: a statistical method, an empirical formula and a model-based technique. This study was the first one to assess the HR-related changes in cf-PWV regardless of BP variation. Following a similar principle to the one adopted in our study, they quantified the HR effect on cf-PWV by assuming a constant aoDBP. The authors performed the correction method on a study population of 52 individuals and calculated an effect equal to 0.2 m/s per 10 bpm. In another study, Tan *et al.* [46] reviewed and analysed the findings of several published experimental studies investigating the acute effects of HR changes on PWV measurements. They found that the average HR dependency of cf-PWV, weighted by study sample size, was 0.30 m/s per 10 bpm (or 0.03 m/s/bpm) [46], which is in line with our findings. Furthermore, in that study, it was revealed that epidemiological studies exploring the association between resting HR and cf-PWV regardless of BP levels have failed to converge, with approximately just half of the examined studies reporting a significant BP-independent association between HR and cf-PWV [46]. In this respect, our study provides additional evidence showing that HR is a relevant factor that should be considered when arterial stiffness is assessed via the cf-PWV measurement.

In addition to the quantification of the HR effect on cf-PWV, our study investigated the HR dependency on cf-PWV for different levels of arterial stiffness. Our results showed that the cf-PWV increase was 40% higher for stiffer ($C = 0.8 \pm 0.3$ ml/mmHg) than more compliant arteries ($C = 1.7 \pm 0.5$ ml/mmHg). This is rather expected if we consider that a more compliant artery will present a lower increase in pressure due to a volume rise than the increase presented by a stiffer artery. At the same time, aorto-brachial PP amplification was lower in the group of high stiffness (1.9 times smaller than the group of low stiffness). Evidence from previous work [47,48] have demonstrated that, in general, central PP appears to be lower (more compliant aorta) than peripheral PP (stiffer periphery). This PP difference often disappears with ageing and hypertension, wherein the arterial tree and especially the elastic arteries (i.e. proximal aorta) becomes stiffer [49].

Moreover, it must be highlighted that, for the total increase in HR by 40 bpm, the consequent increase in cf-PWV (under constant BP levels) by approximately 0.64 and 1.02 m/s for low and high arterial stiffness levels, respectively, is remarkable and clinically relevant. Even more impressive is the respective increase in cf-PWV per 40 bpm increase under free BP-response (which is a more realistic scenario), namely by 2.32 m/s for low and 2.92 m/s for high arterial stiffness levels, respectively. This is mostly based on existing evidence relating these cf-PWV changes with the corresponding theoretical increase in the cardiovascular (CV) and mortality-risk, as predicted by published prospective, longitudinal, studies. Specifically, a previous meta-analysis exploring the predictive value of cf-PWV demonstrated that an increase in aortic PWV by 1.0 m/s corresponds to an age, sex and risk factor adjusted risk increase of 14, 15 and 15% in total CV events, CV mortality and all-cause mortality, respectively [5]. Finally, our findings provide additional evidence in support of the scientific statement from the American Heart Association [50] recommending that HR should be recorded at the time of an arterial stiffness measurement and taken into consideration in analyses involving PWV.

Furthermore, correction of the cf-PWV measurement for resting HR may have significant clinical implications in the occurrence of pharmacologically induced changes in cardiac rhythm. Concretely, several patients suffering from high resting HR are in need for antiarrhythmic drugs to restore a normal heart beat. Assessment of the cardiovascular state in these patients is crucial [51,52]. However, the medication targeting on HR decrease is likely to affect arterial stiffness and thus, lower the measured cf-PWV value. A lower HR would appear concurrently with a lower cf-PWV value, thus hiding the potential cardiovascular risk associated with arterial stiffness. Employment of a correction method would allow for the corrected characterization of arterial stiffness by isolating the potential pharmacologically induced changes in HR and thus optimizing the accuracy of cardiovascular risk assessment and the predictive value of cf-PWV.

A few study limitations should be acknowledged. Nevertheless, synthetic data can be representative of the properties of the real clinical measurements, while they allow for controlling the distribution of rare but relevant conditions or events. Translation of the results from any in-silico study to real conditions and patients cannot be direct, and the extrapolation and application of the theoretical results to clinical practice should be made with great caution. On the contrary, in-silico models allow the control of specific parameters in highly multifactorial problems, which is impossible to be achieved under in-vivo conditions. Finally, the in-silico model that was used in this study has been thoroughly validated against in-vivo data and provides realistic representations of the physiological signals.

In conclusion, the present study estimated the direct effect of HR on cf-PWV independently of the concomitant BP variations. Overall, the BP-independent effect of HR on cf-PWV was estimated to be approximately 0.16 m/s per 10 bpm and 0.26 per 10 bpm in cases with decreased and increased arterial stiffness, respectively. Although small variations in HR appear to have a minimal effect on the cf-PWV measurement, a larger increase in HR may lead to a more significant physiological change in cf-PWV and, hence, to a higher cardiovascular risk. In this respect, our study provided a strong and clinically relevant background for the establishment of cf-PWV correction for HR changes (especially for individuals with increased arterial stiffness) and also for further examination of the combined predictive role of both cf-PWV and HR.

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Conflicts of interest

There are no conflicts of interest.

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