Insulin-Like Growth Factor 1

Revisiting the Relationship Between Blood Pressure and Insulin-Like Growth Factor-1

Aletta Elisabeth Schutte, Massimo Volpe, Giuliano Tocci, Elena Conti

Abstract—Conflicting evidence exists on the relationship between blood pressure (BP) and insulin-like growth factor-1 (IGF-1). We reviewed available articles and pooled extrapolated regression coefficients for the association between BP and total IGF-1 as reported in the literature and included additional data from 912 individuals from the general population. We identified 20 studies including 11,704 subjects. We also measured total IGF-1, insulin-like binding protein-3, and BP in 912 black and white men and women from South Africa (aged 20–70 years). When plotting positive and negative weighted regression coefficients (29 data points) against IGF-1, we found a significant positive relationship (r=0.31; P<0.001; n=11,704) intercepting the 0 point at 191 ng/mL IGF-1, suggesting an inverse BP/IGF-1 relationship in low IGF-1 conditions, and a positive relationship in overtly high IGF-1 conditions. In conclusion, our findings suggest that the relationship between BP and IGF-1 is dependent on, or related to, IGF-1 concentrations, as an expression of direct or reverse causality. Low IGF-1 bioavailability (associated with aging and vascular deterioration), resistance to IGF-1, and the complex interplay between IGF-1 and other vasoactive hormones could mask the vasoprotective functions of IGF-1 in cross-sectional studies or could modify their functions in prospective studies. (Hypertension. 2014;63:1070-1077.)

Online Data Supplement

Key Words: acromegaly ■ aging ■ hypertension ■ vasodilation

Some inconsistencies are still present among published studies that investigated protective versus detrimental cardiovascular effects of insulin-like growth factor-1 (IGF-1). Solid biological evidence supports the potential blood pressure (BP)-lowering effects of IGF-1, which has prompted consideration of recombinant IGF-1 treatment as a potential therapeutic target. Clinical data in IGF-1-deficient experimental animals and humans indicate development of hypertension at lower or therapeutically antagonized IGF-1 levels already from antenatal life, and as a possible product of reduced NO tone, antioxidative capacity, and unbalanced high sympathetic activity.

IGF-1 has important endothelial protective functions mediated mainly by the phosphoinositide 3-kinase (PI3K)/Akt signaling pathway, including vasodilation via NO, re-endothelialization through activated endothelial progenitor cells, plaque stabilizing, anti-inflammatory, and antiplatelet activities. However, the binding of IGF-1 to the IGF-1 receptor also activates the mitogen-activated protein kinase pathway, which drives cellular proliferation, differentiation, and motility—actions related to suggested proatherogenic and carcinogenic activities of IGF-1.

The complexity in understanding the vascular functions of IGF-1 is underscored by conflicting reports on the association between BP and IGF-1. These findings include (1) small studies (n=5) indicating that hypertensive patients had higher IGF-1 concentrations compared with normotensives (total n=250); (2) a neutral or positive relationship between BP and IGF-1 in active acromegalic patients (n=305 and 21, respectively); (3) cross-sectional studies indicating a neutral relationship between BP and IGF-1 (total n=5263); and (4) cross-sectional studies (total n=5771), including Framingham and our own, yielding significant inverse associations between BP and IGF-1 in 544 young black men after 10 years and a 44% reduced risk for incident hypertension in 2046 nondiabetic women over 4 years.

An analysis pooling results from different studies is currently lacking. We, therefore, set out to provide insight into these controversial results by evaluating published regression coefficients for the BP and IGF-1 relationship. We also included additional data of 912 individuals to enable a comparison of cardiometabolic profiles of those within low to high IGF-1 categories.

Research Design and Methods

Literature Review

We searched the literature for articles presenting regression coefficients in the form of single (Pearson or Spearman) or partial regression coefficients for the relationship between systolic or mean BP and total IGF-1 concentrations (n=113).
IGF-1 in populations aged >18 years. Articles reporting free IGF-1, bioactive IGF-1, or IGF-1 expressed as a ratio to IGF-binding proteins were excluded because of scarcity of data. All accessible articles presenting r-values were included in the analyses and plotted against total IGF-1 concentration in nanograms per milliliter (see Figure). For all articles, the relationship of total IGF-1 with systolic BP was provided, except for 1 article that reported mean arterial pressure.19

Study Design and Subject Selection

Included studies were different in design. We considered 3 prospective studies (n=2976),23,27,29 although regression coefficients used were derived from cross-sectional analyses within those studies, 14 cross-sectional studies (n=7798),14,24–26,29–35,37,42 and 3 case–control comparisons (n=930).20,22,28 Overall, the analysis included 11 704 subjects. In these studies, information about ongoing antihypertensive therapy were not always provided, and hence the state of BP treatment was inconsistent across studies.

The above number for cross-sectional studies also included data from 912 black and white men and women from the Sex, Age and Ethnicity on Insulin Sensitivity and Cardiovascular Function (SAfrEIC) and Sympathetic Activity and Ambulatory Blood Pressure in Africans (SABPA) studies, the methods of which are described elsewhere12,43 and more details provided in the online-only Data Supplement.

![Figure. Regression coefficients for the relationship between blood pressure and total insulin-like growth factor-1 (IGF-1) extracted from different studies plotted against total IGF-1 concentration, with (A) unweighed regression analysis and (B) weighed according to sample size: (1) patients with active acromegaly aged 48±9 y; cross-sectional analysis of cases (n=21)22; (2) patients with active acromegaly aged 46.8±14.9 y; cross-sectional analysis of cases at study entry (n=200)20; (3) Sex, Age and Ethnicity on Insulin Sensitivity and Cardiovascular Function (SAfrEIC) study: black and white population aged 31.8±9.32 y; cross-sectional study (n=27), adjusted for age and sex; (4) Sympathetic Activity and Ambulatory Blood Pressure in Africans (SABPA) study: black and white population aged 36.1±11.3 y; cross-sectional study (n=30), adjusted for age and sex; (5) black men aged 27±3.7 y; cross-sectional analysis of year 2 of prospective study (n=544), adjusted for age, body mass index (BMI), physical activity, alcohol, and smoking23; (6) healthy young Finnish men aged 25±5 y; cross-sectional study (n=846), adjusted for age24; (7) white men aged 28±3.4 y; cross-sectional analysis of year 2 of prospective study (n=747), adjusted for age, BMI, physical activity, alcohol, and smoking23; (8) healthy Maori, Samoan, and European adults aged 18 to 50 y; cross-sectional study (n=75)27; (9) Japanese men from the general population aged 51.6±8.6 y; cross-sectional study (n=330)16; (10) healthy Swedish men and women aged 54.7 (40.0–60.2) y; cross-sectional analysis of cohort study (n=715), adjusted for age, sex, and analytic batch25; (11) men from the general population aged 25 to 64 y; cross-sectional analysis (n=197)27; (12) white nondiabetic men and women aged 37±9 y; cross-sectional study (n=110)23; (13) white nondiabetic men and women aged 41±14 y; cross-sectional study (n=186), adjusted for age and sex25; (14) SAfrEIC study: black and white population aged 38.2±12.3 y; cross-sectional study (n=282), adjusted for age and sex; (15) untreated hypertensive men and women aged 51.1±11.6 y; cross-sectional study (n=100)28; (16) white patients with impaired glucose tolerance aged 51.7±10 y; cross-sectional analysis of cases (n=54)38; (17) borderline hypertensive men aged 50±1 y; cross-sectional analysis of cases (n=75)38; (18) SABPA study: black and white population aged 43.9±8.9 y; cross-sectional study (n=269), adjusted for age and sex; (19) white nondiabetic participants aged 47.8±14 y; cross-sectional analysis of controls (n=357)33; (20) white patients with type 2 diabetes mellitus aged 60.1±11 y; cross-sectional analysis of cases (n=58)38; (21) SABPA study: black and white population aged 49.7±8.6 y; cross-sectional study (n=89), adjusted for age and sex; (22) elderly men and postmenopausal women aged 73.9±9.2 y; cross-sectional analysis of baseline in prospective study (n=1185)23; (23) hypertensive men and women and controls aged 50±10 y; cross-sectional analysis of cases and controls combined (n=157)39; (24) SAfrEIC study: black and white population aged 47.6±11.8 y; cross-sectional study (n=215), adjusted for age and sex; (25) women with/without coronary heart disease aged 60 to 79 y; cross-sectional analysis of data from prospective study (n=500), adjusted for age28; (26) women from the general population aged 25 to 64 y; cross-sectional analysis (n=195)37; (27) men and women from the general population aged 45.5±19.4 y; cross-sectional study (n=404), adjusted for age40; (28) healthy men and women aged 46.8±15 y; cross-sectional analysis of controls at study entry (n=200)38; (29) men and women from the general population aged 40±9 y (n=3496); cross-sectional analysis of first examination of prospective study, adjusted for sex and age.38

r=0.39; p=0.037

r=0.31; p<0.001
Statistical Analysis
We plotted regression coefficients (r-values for the relationship between mean or systolic BP and total IGF-1) against total IGF-1 concentration as reported from different studies, including the SAfrEIC and SABPA studies (n=11704). We repeated the analysis by adding weights to regression coefficients based on study sample sizes and performed single linear regression analysis to determine the relationship between reported regression coefficients and IGF-1 concentrations (see Figure, A and B). In the SAfrEIC and SABPA studies, we tested the relationship between systolic BP and total IGF-1 for interactions of age, sex, ethnicity, body mass index, C-reactive protein (CRP), reactive oxygen species (ROS), and γ-glutamyl transference (Table S1 in the online-only Data Supplement). We also categorized the participants from SAfrEIC and SABPA studies into low (mean IGF-1 <100 ng/mL), medium (mean IGF-1, 170–180 ng/mL), and high IGF-1 groups (mean IGF-1, 280–335 ng/mL) with n ranging from 27 to 282 (see Figure). The characteristics of these groups were compared using χ² tests, ANOVA, and analyses of covariance (see Table; Table S2). Non-normally distributed variables were normalized via logarithmic transformation and presented as geometric means (5th and 95th percentiles). Lastly, we created scatterplots of systolic BP against total IGF-1 and IGF-1/insulin-like binding protein-3 (IGFBP-3) ratio using data from SAfrEIC and SABPA studies (n=912), indicating P for trend (ANOVA) between IGF-1 and IGF-1/IGFBP-3 groups (n=41–184; Figure S1).

Results
We plotted (Figure, A) unweighed regression coefficients (r-values for correlation between mean or systolic BP and total IGF-1) against the reported mean total IGF-1 from previous studies,14,20,22–31,33–37,42 as well as the low, middle, and high IGF-1 groups from SAfrEIC and SABPA studies. A similar analysis weighed for study sample size is also presented (Figure, B). The reported studies included a variety of populations, such as patients with active acromegaly,20,22 impaired glucose tolerance or type 2 diabetes mellitus,28 hypertension,42 young and healthy individuals or the general population,23,24,26,33,35 different ethnic groups,26,32 and elderly men and women.29 Ethnicities included participants of European, African, Samoan, and Maori descent. The more prevalent population was, however, that of nonacromegalic adult men and women of white race with or without diabetes mellitus and hypertension (a total of 10147 subjects).

In unweighed linear regression analysis, we found a positive association between mean total IGF-1 reported in each study and regression coefficient (β=0.39; P=0.037; Figure, A). The slope intercepted the y axis at an IGF-1 level of 223.8

Table. Characteristics of Participants From SAfrEIC and SABPA Studies, According to Low to High Concentrations IGF-1 Groups

<table>
<thead>
<tr>
<th>Total IGF-1 Groups</th>
<th>Low</th>
<th>Middle</th>
<th>High</th>
<th>P for Trend</th>
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<tbody>
<tr>
<td>SAfrEIC study</td>
<td></td>
<td></td>
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<tr>
<td>Age, y</td>
<td>47.7±0.81</td>
<td>38.2±0.71</td>
<td>31.8±2.30</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Women, %</td>
<td>47.9</td>
<td>49.1</td>
<td>40.74</td>
<td>0.70</td>
</tr>
<tr>
<td>Africans, %</td>
<td>49.8</td>
<td>35.7</td>
<td>7.41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted for age, sex, ethnicity</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>IGF-1/IGFBP-3</td>
<td>0.65±0.02</td>
<td>1.23±0.02</td>
<td>1.99±0.06</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>IGFBP-3, nmol/L</td>
<td>133±1.89</td>
<td>152±1.47</td>
<td>161±4.81</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Insulin, μU/mL</td>
<td>5.51 (4.66; 6.23)</td>
<td>7.59 (6.89; 8.37)</td>
<td>6.02 (4.33; 8.37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>122±1.24</td>
<td>121±0.96</td>
<td>118±3.15</td>
<td>0.44</td>
</tr>
</tbody>
</table>

SABPA study

| Limits of IGF-1, ng/mL | 25.7–110 | 111–246 | 247–372 |            |
| Age, y                | 49.7±0.97 | 43.9±0.56 | 36.1±1.67 | <0.001* |
| Women, %              | 58.4 | 49.4 | 46.7 | 0.29 |
| Africans, %           | 62.9 | 65.9 | 2.79 | <0.001 |
| Adjusted for age, sex, ethnicity |     |        |      |            |
| IGF-1/IGFBP-3        | 0.76±0.03 | 1.25±0.02 | 1.85±0.05 | <0.001* |
| IGFBP-3, nmol/L      | 122±2.72 | 141±1.44 | 151±4.45 | <0.001* |
| Ambulatory systolic BP, mmHg | 129±1.57 | 127±0.83 | 126±2.57 | 0.34 |
| Carotid IMT, mm†      | 0.64±0.01 | 0.65±0.01 | 0.66±0.02 | 0.63 |
| C-reactive protein, mg/L | 4.11 (3.29; 5.14) | 2.49 (2.21; 2.80) | 2.88 (2.00; 4.16) | <0.001* |
| γ-glutamyl transference, U‡ | 31.7 (27.3; 36.7) | 27.0 (24.9; 29.3) | 22.0 (17.3; 28.1) | 0.044* |
| Reactive oxygen species, U‡ | 105±2.79 | 89±2.18 | 66±4.55 | <0.001* |

Data are arithmetic mean±SE or geometric mean (5th and 95th percentile intervals) for logarithmically transformed variables. BP indicates blood pressure; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor binding protein-3; IMT, intima-media thickness; SABPA, Sympathetic Activity and Ambulatory Blood Pressure in Africans; and SAfrEIC, Sex, Age and Ethnicity on Insulin Sensitivity and Cardiovascular Function.

*Significant difference between Low and High groups.
†Additionally adjusted for mean arterial pressure.
‡Unit: 1 mg H2O2/L.

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ng/mL. When adding weights according to study sample sizes (Figure, B), the association remained significant ($r=0.31; P<0.0001$) and intercepted the y axis at 191.0 ng/mL.

Younger and acromegalic populations were preferentially distributed rightward with respect to the intercept and upward with respect to the tendency line, denoting a more frequent positive relationship between BP and IGF-1. Conversely, more aged and nonendocrine-diseased subgroups dispersed more frequently leftward with respect to the intercept and downward with respect to the tendency line, denoting a more frequent negative relationship between BP and IGF-1.

In sensitivity analyses, we excluded active acromegalic study populations who reported IGF-1 $>420$ ng/mL from weighed regression analyses and confirmed the previous finding ($r=0.32; P<0.001$). A similar result was found when excluding the 6 regression coefficients from SAfrEIC and SABPA studies ($r=0.34; P<0.001$).

We found no significant interactions of age ($P=0.66$), sex ($P=0.81$), ethnicity ($P=0.92$), or antihypertensive medication ($P=0.18$) on the relationship between systolic BP and IGF-1 in SAfrEIC and SABPA studies (Table S1). However, we found significant interactions of body mass index ($P=0.011$), CRP ($P=0.012$), ROS ($P<0.001$), and $\gamma$-glutamyl transferase ($P=0.009$) on BP/IGF-1 relationship.

We compared the cardiovascular and biochemical profiles of low to high IGF-1 groups from SAfrEIC and SABPA studies (see Table; Table S2). Both studies demonstrate that with increasing total IGF-1 levels, the IGF-1/IGFBP-3 ratio as well as the IGFBP-3 level increased ($P<0.001$). Groups with elevated IGF-1 in both studies also presented a favorable health profile, namely younger ages ($P<0.001$), and lower levels of ROS ($P<0.004$) and $\gamma$-glutamyl transferase ($P<0.044$). There was no sex differentiation between different IGF-1 groups, but the proportion of black participants decreased ($P<0.001$) with increasing IGF-1 levels. There were no differences in systolic or diastolic BP in different IGF-1 groups ($P>0.34$), and no differences in carotid intima-media thickness in the SABPA study ($P=0.63$).

Lastly, we plotted total IGF-1 and IGF-1/IGFBP-3 against continuous systolic BP for the 912 participants (Figure S1). Single linear regression analyses indicated a significant negative association of systolic BP with total IGF-1 ($r=-0.17; P<0.001$) and with IGF-1/IGFBP-3 ratio ($r=-0.20; P<0.001$). In the elevated IGF-1 subgroup, that is, total IGF-1 $>220$ ng/mL, the significance was lost ($r=0.08; P=0.33$; n=164). This was also seen for IGF-1/IGFBP-3 ratio $>1.6$ ($r=-0.01; P=0.92$; n=134).

Discussion

Our results indicate that the cross-sectional relationship between BP and IGF-1 is dependent on total IGF-1 concentrations. This was revealed via graphic exposition of weighed regression coefficients for the BP and IGF-1 relationship from various studies, notwithstanding the heterogeneous populations from which the results were obtained, including patients with acromegaly, type 2 diabetes mellitus, hypertension, and young and healthy individuals. This type of interaction could likely denote 2 potential, alternative, and not mutually exclusive explanations.

The first could imply a U-shaped relation between IGF-1 and antihypertensive activity, which was also reported for associations between IGF-1 and cardiovascular mortality or insulin resistance. This is supported by significant negative associations in populations within the lower total IGF-1 ranges and by weak or neutral associations shown for those reporting IGF-1 levels in the midranges of $=190$ to 224 ng/mL (slope intercept at the y axis). This proposed U- or J-shaped relationship is partially supported by our scatterplot (Figure S1) with total IGF-1 and bioavailable IGF-1 (IGF-1/IGFBP-3) plotted against systolic BP in 912 individuals. In the whole group, we found significant negative associations. However, in those with IGF-1 $>220$ ng/mL, no significant associations were found between BP and total or bioavailable IGF-1 ($r=-0.08$ and $-0.01$, respectively), suggesting a plateau.

The second and more likely explanation for our findings could indicate an ongoing phenomenon of IGF-1 resistance developing at high IGF-1 levels. The significant linear association found between cross-sectional IGF-1 concentrations and reported regression coefficients indicates that with increasing IGF-1 levels the relation between this hormone and BP would change from negative to positive.

Given the direct vasodilatory antihypertensive effect achieved by IGF-1 on intravenous administration, the changing cross-sectional BP association with increasing IGF-1 denotes a phenomenon of IGF-1 resistance, supported in our SABPA and SAfrEIC studies by a positive interaction between the investigated association and CRP, body mass index and $\gamma$-glutamyl transferase, all indices of metabolic derangements. IGF-1 resistance has been observed in dysmetabolic states such as chronic renal failure, with increased compensatory serum IGF-1 aiming at overcoming IGF-1 signaling defects. Chronic renal failure is a prototypical state of reduced IGF-1 sensitivity, otherwise able to increase glomerular filtration rate, effectively delaying the beginning of hemodialysis. Resistance training improved IGF-1 sensitivity, thus confirming the state of IGF-1 resistance as causal for the described cross-sectional association between higher IGF-1 levels and chronic renal failure.

We propose these 2 explanations for our findings, namely either a U-shaped relationship or the development of IGF-1 resistance, which have to be interpreted within the context of limitations and strengths of our study. Our explanations are based on cross-sectional analyses not suitable to infer causality. We found and included only 3 prospective studies assessing IGF-1 with BP, for a total of 3837 subjects and 23,094 person-years of follow-up. These studies found no prohypertensive effect of IGF-1 and indicated IGF-1 either as protective (4 years); for age-adjusted African men, 10 years or neutral (4 years; for whites, 2, 7, 10 years) as to hypertension onset, at both medium- and long-term follow-up times.

Apart from methodological considerations, clarification of the biological role of IGF-1 in BP regulation may be obscured by the complex mechanisms involved in maintaining IGF-1 tissue bioavailability. IGF-1 expression and function are under the control of growth hormone (GH), which declines with age;
of IGF-1 binding to 6 different binding proteins (with 80% of total IGF-1 bound by IGFBP-3); of genetic and environmental modulation (eg, diet and alcohol intake); as well as of the interplay with other endocrine factors (insulin and thyroid hormone increase IGF-1, and glucocorticoids induce IGF-1 resistance), thus drawing an age-related variability of the endocrine milieu conditioning IGF-1. Nevertheless, the biological vascular protective role of IGF-1 is clearly described and conserved through different ages, indicating that the vasodilatory and BP-lowering effects of IGF-1 are achieved by inducing NO synthesis. The lack of associations observed between BP and IGF-1 in healthy populations may be explained by a homeostatic balance obtained in maintaining normal BP levels.

Conditions presenting abnormally high total or free IGF-1 levels are rare. IGF-1 normally reaches its peak levels in puberty and show a consistent decrease with advancing age. Our results suggest a more frequent distribution of young and acromegalic in the positive regions of the dose–response curve of IGF-1 levels regarding its association with BP, suggesting a dampened antihypertensive (or increased resistance to) effect of IGF-1 in these subgroups. Previous results in boys aged 11 to 18 years similarly found significant independent positive relationships between BP and IGF-1. Conversely, patients with active acromegaly present severely elevated GH and IGF-1 levels, but also exhibit a mixed endocrine disorder, with associated hyperinsulinemia and hyperglycagomia, which per se significantly impair vascular function. In these patients, hypertension and postoperative IGF-1 levels were even found insignificantly protective with respect to mortality, whereas malignancy and age were found as the main outcome predictors. The lower ratio of bioavailable IGF-1, controlling microcirculation and vascular resistances, to GH, controlling muscle mass, seems to induce a relative rarefaction of microcirculation, responsible for hypertension in this and perhaps other conditions of rapidly increasing growing muscle mass (as in adolescents and children). These results support the notion that elevated BP in acromegaly and perhaps growing adolescents and children may be because of elevated GH levels, excessively counterbalancing available IGF-1 levels. In these conditions, IGF-1 may be inadequate to provide a sufficient distal vascularization of increasing muscle mass, with ensuing hypertension. Moreover, high GH levels exert a hypertensive action through expansion of the plasma volume by a sodium-retaining effect on the kidney.

On the other hand, we found a more frequent distribution of older and dysmetabolic patients in the negative regions of the dose–response curve of IGF-1 levels with respect to its association with BP, suggesting an antihypertensive (or reduced resistance to) effect of IGF-1 in these subgroups. Opposed to elevated IGF-1 in acromegaly, the disruption of homeostatic BP and IGF-1 balance is also described during low IGF-1 levels, where significant negative associations with BP were observed. This end of the scale generally represents older age and chronic diseases of lifestyle, also including hypertension, coronary heart disease, and patients with impaired fasting glucose or type 2 diabetes mellitus.

In these subgroups, including those with GH insensitivity but also normal subjects, acute and chronic recombinant human IGF-1 administration did not cause hypertension, conversely lowers BP (especially mean and diastolic BP), and increases renal filtration rate by 100%.

Our data show that at low serum concentrations the beneficial vasodilatory and vasoprotective functions of IGF-1 are still exerted and apparently strengthened. In this case, however, they may be even more easily dampened when increased angiotensin II opposes IGF-1 by interfering with the PI3K pathway, resulting in BP elevation, sodium retention, and excessive production of ROS. The low IGF-1 groups from both SAfrEIC and SABPA studies presented the highest levels of ROS and inflammation (CRP), thus suggesting a net loss of anti-inflammatory and endothelial protective functions of IGF-1.

Our study is limited by a relatively low number of publications reporting regression coefficients for the BP and IGF-1 relationship in conditions with high IGF-1 levels, as well as by a low number of prospective longitudinal studies. Moreover, collected studies lacked data regarding anti-hypertensive therapy, which has been proved to increase both IGF-1 levels and myocardial tissue IGF-1 signaling, as well as the opposite. Our interaction analyses, however, indicated no mediation of antihypertensive therapy on the BP/IGF-1 relationship.

To conclude, our findings suggest that the relationship between BP and IGF-1 is dependent on or reflected by the IGF-1 concentration, as an expression of direct or reverse causality. Low IGF-1 bioavailability (associated with aging and vascular deterioration), resistance to IGF-1 in dysmetabolic states, and the complex interplay between IGF-1 and other vasoactive hormones could mask the vasoprotective functions of IGF-1 in cross-sectional studies or could modify their functions in prospective studies. Prospective or interventional controlled studies are, therefore, welcome to definitely dissect this conundrum, as recombinant human IGF-1 treatment to elevate IGF-1 to optimal levels may result as an effective tool in cardiovascular medicine to improve vascular function.

Perspectives
Our results confirm a possible antihypertensive effect to be added to the desirable cardiovascular benefits of IGF-1, in selected populations, with possible tolerance or an enhancement effect with changing serum concentrations. This encourages consideration of studies on recombinant IGF-1 treatment as a potential therapeutic target. Notwithstanding the beneficial effects of PI3K-like activities of IGF-1, the activation of its mitogen-activated protein kinase signaling pathway, implicated in cancer, cell growth, and proliferation, requires a pharmacological blunting such as that provided by adenosine and by metformin. Opportunity to enhance the beneficial PI3K-like intracellular pathway of IGF-1, without the harmful mitogen-activated protein kinase effect, requires further consideration.

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Disclosures
None.

References

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Novelty and Significance

What Is New?
• Inconclusive findings exist in literature on the vasoprotective versus adverse effects of insulin-like growth factor-1 (IGF-1). This is specifically true for the effect of IGF-1 on blood pressure (BP). By synthesizing the regression coefficients for the BP/IGF-1 relationship from literature and by including new data from 912 subjects (totaling n=11,704), we found an inverse BP/IGF-1 relationship in low IGF-1 conditions, and a positive relationship in overtly high IGF-1 conditions.

What Is Relevant?
• These findings suggest that the cross-sectional relationship between BP and IGF-1 is dependent on (or related to) the IGF-1 concentration. The vasoprotective functions of IGF-1 may be masked in conditions of low IGF-1 bioavailability (associated with aging and chronic diseases of lifestyle) or when resistance to IGF-1 occurs in dysmetabolic states.

Summary
Our findings impart that the beneficial vasodilatory effect of IGF-1 is (1) attenuated in individuals with impaired vascular function (such as hypertensives and the elderly) because of low IGF-1 bioavailability, and (2) attenuated in individuals with overtly high IGF-1 concentrations (such as adolescents or acromegalic patients) because of IGF-1 resistance or reduction with respect to muscle mass. Because of the ever increasing prevalence of chronic diseases resembling low IGF-1 bioavailability, the desirable cardiovascular benefits of IGF-1 should be considered as a potential therapeutic target in select populations.
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REVISITING THE RELATIONSHIP BETWEEN BLOOD PRESSURE AND INSULIN-LIKE GROWTH FACTOR-1

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Methods: Supplement

The SAfrEIC study (South African study regarding the role of Sex, Age and Ethnicity on Insulin sensitivity and Cardiovascular function) included 750 asymptomatic black and white volunteers from both sexes (aged 20 to 70 years). We included a sub-sample of 211 black and 316 white participants based on the following exclusion criteria:\textsuperscript{26} non-fasting (N=46), oral contraceptive use (N=48), missing data (N=29), previous serious chronic illness except hypertension, e.g. diabetes (N=2) or HIV infection (N=98). The SABPA (Sympathetic activity and Ambulatory Blood Pressure in Africans) study included 409 black and white school teachers (aged 25 to 65 years).\textsuperscript{37} We excluded HIV-infected individuals (N=19) leaving a sub-sample of 179 black and 209 white men and women. Approval was obtained from the Ethics Committee of the North-West University for both the SAfrEIC and SABPA studies. All participants gave informed consent. The study complied with all applicable requirements of U.S. and international regulations, in particular the Declaration of Helsinki.
Table S1 Multiple regression models to test for interactions of different factors on the relationship between systolic BP and total IGF-1 in the SAfrEIC and SABPA studies (N=912)

<table>
<thead>
<tr>
<th>Model</th>
<th>Main independent variable</th>
<th>β</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IGF-1 (log) x age</td>
<td>-0.12</td>
<td>0.27</td>
<td>0.66</td>
</tr>
<tr>
<td>2</td>
<td>IGF-1 (log) x sex</td>
<td>0.07</td>
<td>0.31</td>
<td>0.81</td>
</tr>
<tr>
<td>3</td>
<td>IGF-1 (log) x ethnicity</td>
<td>0.03</td>
<td>0.34</td>
<td>0.92</td>
</tr>
<tr>
<td>4</td>
<td>IGF-1 (log) x body mass index</td>
<td>0.80</td>
<td>0.31</td>
<td>0.011</td>
</tr>
<tr>
<td>5</td>
<td>IGF-1 (log) x C-reactive protein (log)</td>
<td>0.72</td>
<td>0.29</td>
<td>0.012</td>
</tr>
<tr>
<td>6</td>
<td>IGF-1 (log) x reactive oxygen species (log)</td>
<td>2.43</td>
<td>0.51</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>7</td>
<td>IGF-1 (log) x γ-glutamyl transferase (log)</td>
<td>0.66</td>
<td>0.25</td>
<td>0.009</td>
</tr>
<tr>
<td>8</td>
<td>IGF-1 (log) x antihypertensive therapy</td>
<td>0.39</td>
<td>0.29</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Other independent variables in each model include log IGF-1, study batch (SAfrEIC or SABPA) and either age, sex, ethnicity, body mass index, C-reactive protein, reactive oxygen species, γ-glutamyl transferase or antihypertensive therapy depending on the interaction tested.

Bold text denotes statistical significance (P<0.05)
Table S2 Detailed characteristics of participants from the SAfrEIC and SABPA studies, according to low to high concentration IGF-1 groups

<table>
<thead>
<tr>
<th>Total IGF-1 groups</th>
<th>Low (N=215)</th>
<th>Middle (N=282)</th>
<th>High (N=27)</th>
<th>( p ) for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limits of IGF-1 (ng/mL)</td>
<td>4.99-109</td>
<td>110-289</td>
<td>292-487</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>47.7 ± 0.81</td>
<td>38.2 ± 0.71</td>
<td>31.8 ± 2.30</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Sex (Women, %)</td>
<td>47.9</td>
<td>49.1</td>
<td>40.74</td>
<td>0.70</td>
</tr>
<tr>
<td>Ethnicity (Africans, %)</td>
<td>49.8</td>
<td>35.7</td>
<td>7.41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>84.7 ± 1.04</td>
<td>85.1 ± 0.91</td>
<td>82.4 ± 2.94</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Adjusted for age, sex, ethnicity

<table>
<thead>
<tr>
<th></th>
<th>Low (N=215)</th>
<th>Middle (N=282)</th>
<th>High (N=27)</th>
<th>( p ) for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-1/IGFBP-3</td>
<td>0.65 ± 0.02</td>
<td>1.23 ± 0.02</td>
<td>1.99 ± 0.06</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>IGFBP-3 (nmol/L)</td>
<td>133 ± 1.89</td>
<td>152 ± 1.47</td>
<td>161 ± 4.81</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Insulin (µU/mL)</td>
<td>5.51</td>
<td>7.59</td>
<td>6.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>[4.66; 6.23]</td>
<td>[6.89; 8.37]</td>
<td>[4.33; 8.37]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>122 ± 1.24</td>
<td>121 ± 0.96</td>
<td>118 ± 3.15</td>
<td>0.44</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>79.4 ± 0.81</td>
<td>80.2 ± 0.63</td>
<td>78.2 ± 2.05</td>
<td>0.52</td>
</tr>
<tr>
<td>Pulse wave velocity (m/s)†</td>
<td>7.92 ± 0.08</td>
<td>7.79 ± 0.06</td>
<td>7.89 ± 0.20</td>
<td>0.43</td>
</tr>
<tr>
<td>Arterial compliance (ml/mmHg)‡</td>
<td>1.99 ±0.02</td>
<td>2.04 ± 0.02</td>
<td>2.09 ± 0.06</td>
<td>0.25</td>
</tr>
<tr>
<td>Total/HDL-cholesterol ratio</td>
<td>3.62</td>
<td>3.97</td>
<td>3.65</td>
<td>0.015</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>1.67</td>
<td>1.27</td>
<td>0.82</td>
<td>0.097</td>
</tr>
<tr>
<td>Reactive oxygen species (U)§</td>
<td>85.0</td>
<td>79.2</td>
<td>75.2</td>
<td>0.004*</td>
</tr>
<tr>
<td>Smoking (yes, %)</td>
<td>47.9</td>
<td>28.5</td>
<td>14.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>γ-glutamyltransferase (U/L)</td>
<td>45.1</td>
<td>36.4</td>
<td>33.3</td>
<td>0.007*</td>
</tr>
</tbody>
</table>

SABPA study

<table>
<thead>
<tr>
<th></th>
<th>Low (N=89)</th>
<th>Middle (N=269)</th>
<th>High (N=30)</th>
<th>( p ) for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limits of IGF-1 (ng/mL)</td>
<td>25.7-110</td>
<td>111-246</td>
<td>247-372</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>49.7 ± 0.97</td>
<td>43.9 ± 0.56</td>
<td>36.1 ± 1.67</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Sex (Women, %)</td>
<td>58.4</td>
<td>49.4</td>
<td>46.7</td>
<td>0.29</td>
</tr>
<tr>
<td>Ethnicity (Africans, %)</td>
<td>62.9</td>
<td>65.9</td>
<td>2.79</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>97.4 ± 1.68</td>
<td>92.2 ± 0.97</td>
<td>92.4 ± 2.89</td>
<td>0.027</td>
</tr>
</tbody>
</table>

Adjusted for age, sex, ethnicity

<table>
<thead>
<tr>
<th></th>
<th>Low (N=89)</th>
<th>Middle (N=269)</th>
<th>High (N=30)</th>
<th>( p ) for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-1/IGFBP-3</td>
<td>0.76 ± 0.03</td>
<td>1.25 ± 0.02</td>
<td>1.85 ± 0.05</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>IGFBP-3 (nmol/L)</td>
<td>122 ± 2.72</td>
<td>141 ± 1.44</td>
<td>151 ± 4.45</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Ambulatory Systolic BP (mmHg)</td>
<td>129 ± 1.57</td>
<td>127 ± 0.83</td>
<td>126 ± 2.57</td>
<td>0.34</td>
</tr>
<tr>
<td>Parameter</td>
<td>Group A</td>
<td>Group B</td>
<td>Group C</td>
<td>p-value</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
<td>---------</td>
</tr>
<tr>
<td>Ambulatory Diastolic BP (mmHg)</td>
<td>79.9 ± 1.00</td>
<td>79.0 ± 0.53</td>
<td>77.3 ± 1.65</td>
<td>0.42</td>
</tr>
<tr>
<td>Pulse wave velocity (m/s)†</td>
<td>7.78 ± 0.17</td>
<td>8.27 ± 0.09</td>
<td>8.56 ± 0.28</td>
<td>0.024</td>
</tr>
<tr>
<td>Arterial compliance (ml/mmHg)‡</td>
<td>1.98 ± 0.04</td>
<td>2.07 ± 0.2</td>
<td>2.18 ± 0.06</td>
<td>0.018*</td>
</tr>
<tr>
<td>Carotid IMT (mm)‡</td>
<td>0.64 ± 0.01</td>
<td>0.65 ± 0.01</td>
<td>0.66 ± 0.02</td>
<td>0.63</td>
</tr>
<tr>
<td>Total/HDL-cholesterol ratio</td>
<td>4.89 ± 0.20</td>
<td>4.73 ± 0.10</td>
<td>4.80 ± 0.32</td>
<td>0.74</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>4.11</td>
<td>2.49</td>
<td>2.88</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Glycated haemoglobin (%)</td>
<td>[5.71; 5.86]</td>
<td>[5.59; 5.74]</td>
<td>[5.39; 5.88]</td>
<td>0.83</td>
</tr>
<tr>
<td>Reactive oxygen species (U)§</td>
<td>105 ± 2.79</td>
<td>89.2 ± 1.48</td>
<td>86.6 ± 4.55</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Smoking (yes, %)</td>
<td>15.9</td>
<td>13.4</td>
<td>13.8</td>
<td>0.15</td>
</tr>
<tr>
<td>γ-glutamyltransferase (U/L)</td>
<td>[31.7; 36.7]</td>
<td>[27.0; 29.3]</td>
<td>[17.3; 28.1]</td>
<td>0.044*</td>
</tr>
<tr>
<td>Physical activity (kcal)</td>
<td>3000</td>
<td>2748</td>
<td>2802</td>
<td>0.18</td>
</tr>
</tbody>
</table>

*indicates significant difference between group (a) and (c).
†Additionally adjusted for mean arterial pressure
‡Additionally adjusted for body mass index
§Unit = 1 mgH₂O₂/liter

Data are arithmetic mean ± SE or geometric mean (5th and 95th percentile intervals) for logarithmically transformed variables. N, number of participants; IGF-1, Insulin-like growth factor-1; IGFBP-3, insulin-like growth factor binding protein-3; BP, blood pressure; HDL-cholesterol, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment insulin resistance; IMT, intima-media thickness
Figure S1 IGF-1 and IGF-1/IGFBP-3 plotted against systolic blood pressure in the general population (SABPA and SAfEIC studies, N=912)