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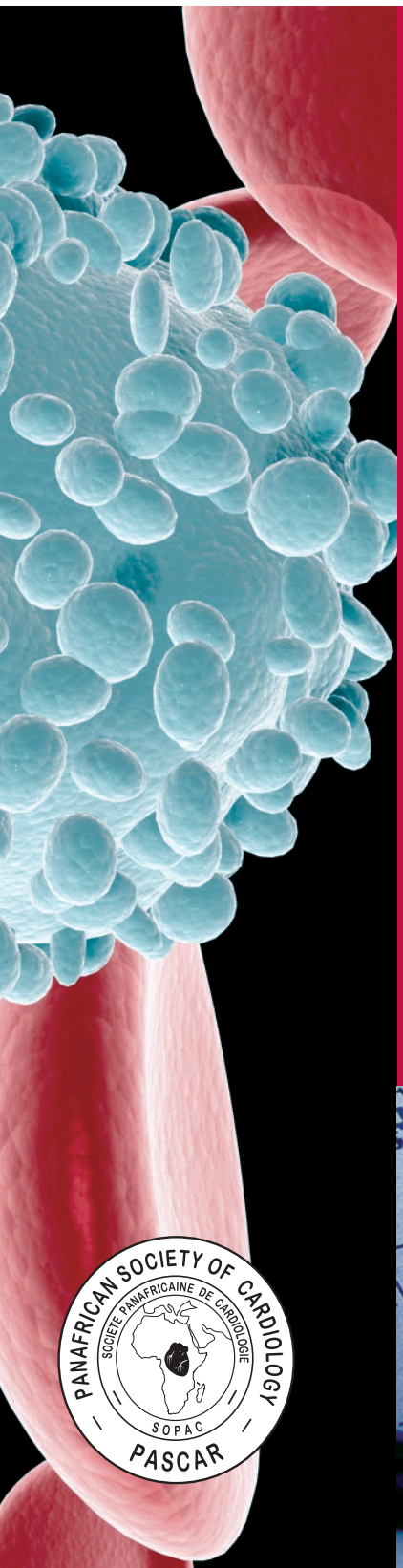

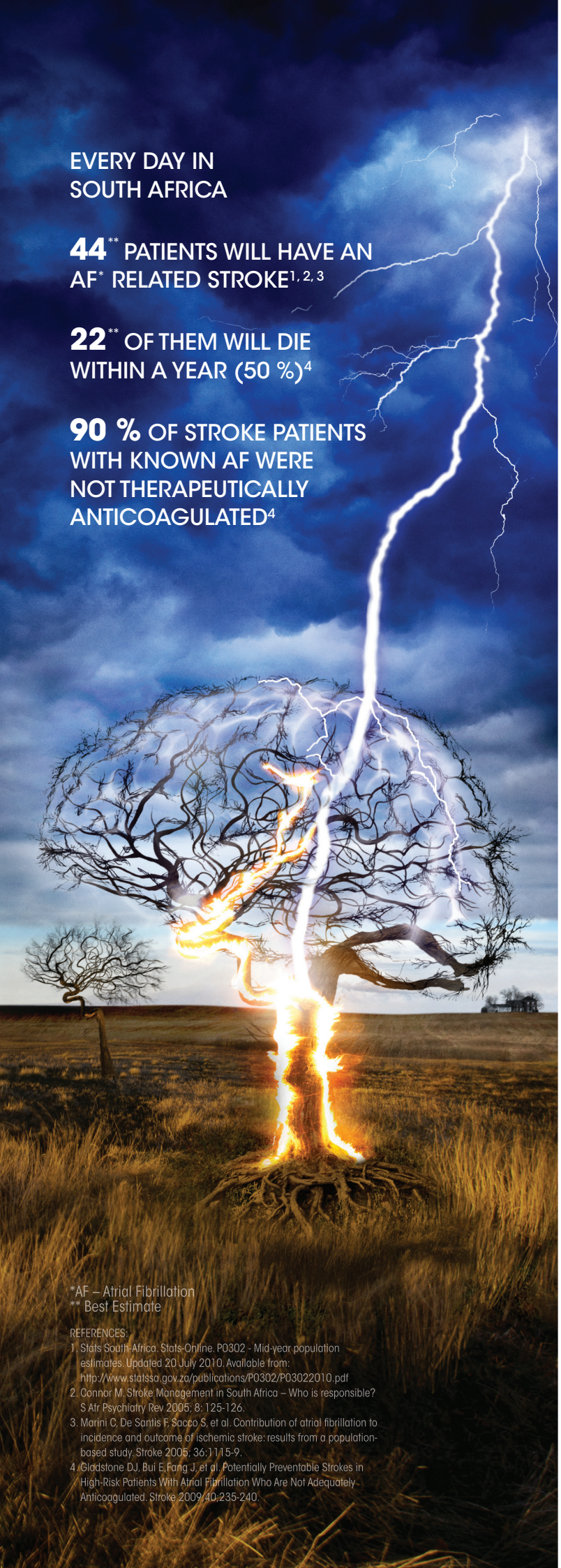

*AF – Atrial Fibrillation
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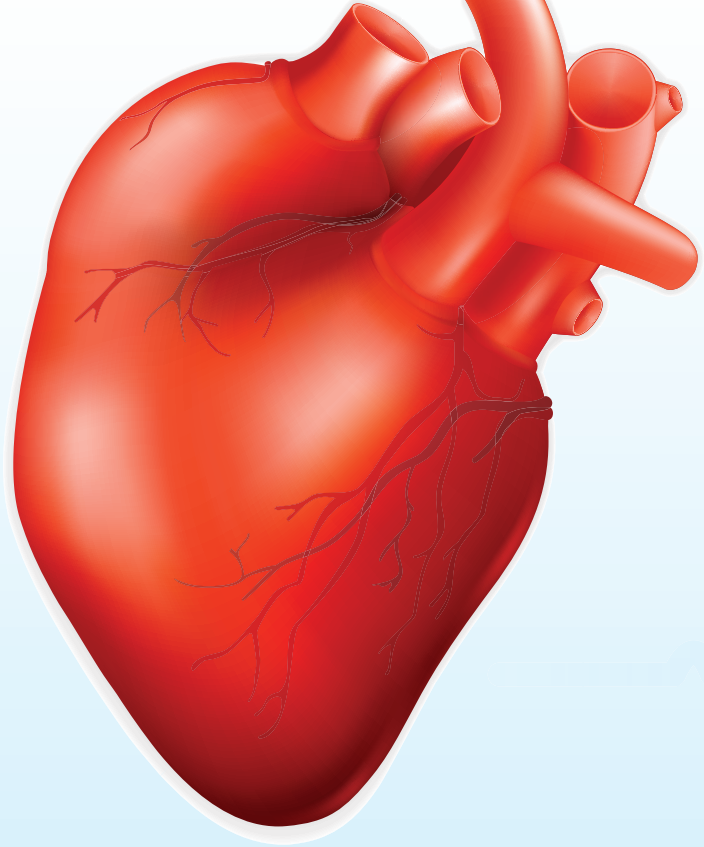

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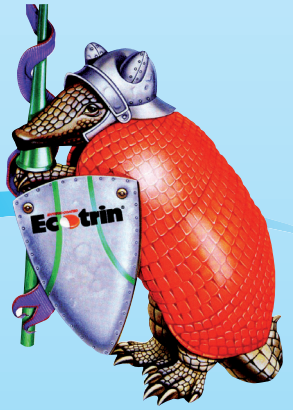

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Editorial

Publication subsidies: challenges and dilemmas facing South African researchers

ANGELA J WOODIWISS

Abstract

In an attempt to encourage and enhance research productivity in higher educational institutions, various systems have been introduced. Currently in South Africa, a government subsidy is granted to higher educational institutions in reward for research outputs (primarily journal publications and postgraduate student graduations). The purpose of this article is not to attack the current or past publication subsidy systems but rather to enlighten researchers, especially emerging researchers, on the benefits and risks of the publication subsidy systems and other systems used to encourage research outputs.

With this aim in mind, a comparison of the current versus the previous South African funding formulae will be made and the positive and negative impacts of these formulae (focusing primarily on the one currently in use) will be discussed in the light of international experiences using similar such approaches. In essence I wish to highlight the challenges and dilemmas faced by South African researchers and higher education institutions as they strive to find ways to increase research outputs while simultaneously sustaining or enhancing the quality and impact of these research outputs, in order to maintain and/or gain national and international recognition.

Keywords: publication subsidy, Department of Higher Education and Training subsidy formulae, research outputs, higher education institutions

There is no doubt that the reputation, both national and international, of a higher educational institution is entrenched in its research profile, which depends to a major extent on its publications and the citations of these publications. Consequently, in aspiring to maintain and/or gain high-level profiles, all higher educational institutions strive to increase research outputs.

In South Africa, as in other countries, the Department of Higher Education and Training, in part to justify public expenditure (to provide greater accountability for the use of research funds), endorses these goals. Moreover, bearing in mind the academic adage 'publish or perish', individual researchers strive to maintain and/or increase their publication outputs. Indeed, in addition to a researcher's reputation (both nationally and internationally) in a particular research field, successful attainment of grant funding as well as promotion are intimately linked to research outputs.

Like many countries around the world, South Africa has a system aimed to incentivise researchers and hence higher educational institutions to increase research outputs.[1-8] The details of the South African systems (the previous system compared to the present system)[8] will be discussed and then compared to those used by other institutions worldwide.[1-7] There have been many criticisms raised against the various systems used to encourage research productivity within the different higher educational institutions worldwide. Indeed, a commentary on the politics of publication, published in *Nature* in 2003,[9] incited a barrage of correspondence both in support of,[6,10,11] and against[12-14] various assessments of research outputs.

As it is advisable to avoid previous shortfalls in systems, especially those which may have long-lasting impacts on the reputation of a higher educational institution,[3] it is important to consider these criticisms and their possible relevance in the context of the current South African system. Hence, the positive versus the negative impacts of the various systems used worldwide will be debated.

The system currently used to encourage research productivity by South African researchers at higher educational institutions is largely intended to be a financial reward-based system.[8] Hence, the financial value (past and present) of research outputs will be presented. Comparisons will be made of the declining percentage of public expenditure on higher education as a percentage of the gross domestic product (GDP) in South Africa versus other countries in Africa,[15] as well as worldwide.[15-17] Moreover, as the intent of the South African system is to reward and hence encourage individual researchers,[8] the differential distribution of the funds both between and within the different South African higher educational institutions will be described.

Bearing in mind the controversies raised against the various assessment systems used worldwide, the potential impact of possible declines in the financial value of research output units, and the potential inequity as a consequence of differential distribution practices within and between higher education institutions in South Africa, some proposals for the way forward will be presented.

Comparison of subsidy formulae used in South Africa

In South Africa, government subsidies to higher educational institutions were previously (from 1987 to 2003) based on the South African post-secondary school (SAPSE) subsidy formula.[8,15] The 1997 White Paper on Higher Education Transformation[18] rejected this model and proposed its replacement with a new model aimed to bring equity and efficiency into the higher educational system.[8] One of the main concerns with the SAPSE

subsidy formula was the efficiency of outputs and outcomes, given that 50% of the formula was input driven.[8]

In 2004, the new funding formula (NFF) was implemented. As one of the ideas behind the NFF was to recognise the importance of research output,[8] the NFF was intended to try and reverse the trend for a decline in research productivity. Indeed, research productivity by higher educational institutions was noted to have declined by 20% from 1997 to 2003.[15]

The SAPSE subsidy formula

Using the SAPSE subsidy formula, the extent of subsidy payments to a higher educational institution was determined on a 50:50 weighting between inputs (predicted costs of student training and research) and outputs (student graduations, publications).[16] The government subsidy was based on the determination of the actual costs of a reasonably efficient higher educational institution and decisions were made on which of these costs should be covered by government subsidies. The values attributed to the various cost units changed each year in accordance with inflation and changing cost patterns. For example, total actual government funding to higher educational institutions increased from R7 532 million in 2001/2 to R7 969 million in 2002/3.[8]

The NFF subsidy formula

Using the NFF, the extent of subsidy consists of four block grants:[8]

- Teaching input grant (planned full-time equivalent student enrollments)
  - Includes provision for research training
- Teaching output grant (non-research graduates produced)
  - Includes provision for research training
- Research output grant (publications and postgraduates produced)
- Grant for other institutional factors (development).

Although the NFF was intended to be based on outputs to a greater extent than the SAPSE, this is not the case. If one considers the four block grants upon which the NFF is based, then indeed outputs contribute more than inputs. However, the percentage of the grant which makes up each of these blocks differs substantially. For example, in 2006 the percentages were: teaching input grant 65%; teaching output grant 15%; research output grant 13%; and grant for other institutional factors 7%.[16] Furthermore, when one considers that both the teaching output grant and the research output grant include subsidies for poor performance, then a proportion of these already relatively small output grants are actually input grants.[16] Hence, the NFF is to a larger extent than the SAPSE driven by input factors.[19]

The research output grant is based on units, whereby a publication in an accredited journal (see section titled 'What constitutes an accredited journal') is one unit; graduation of a student with an MSc by research is one unit; graduation of a student with an MSc by course work and short report is 0.5 unit (if the research component contributes 50%); and graduation of a student with a PhD is three units.[8,20]

A basis of the NFF is that the government first decides how much it can afford to spend on higher education and then it allocates funds according to its needs and priorities.[8] Hence, in the NFF, it was initially proposed that the value per unit output was determined by the total funds available, divided by the total unit output. However, it was recognised that if the total funds available were set in advance, then an increase in total unit output would result in a decrease in the rand value per unit; hence the NFF would create a disincentive to increase research outputs.[8]

The proposal was therefore revised such that the value per unit is determined by:[8]

- setting a benchmark of weighted research output units per full-time permanent academic/research staff [weighted 1.2 for universities (recently increased to 1.4125) and 0.5 for universities of technology] (termed weighted research output)
- generating normative data of total outputs per year by relating above benchmarks per year to staff complements per year (termed normed research output)
- dividing the total government funds available for research outputs by normative total outputs.

In other words, each institution's 'delivery' is determined by expressing their weighted research output as a percentage of their normed research output.[20] The actual subsidy earned by an institution is equal to the institution's weighted research output multiplied by the total government funds available for research outputs and divided by the average normed research output for all institutions.[20]

Of concern is that an institution with a delivery of less than 100% earns a developmental grant that is linearly related to the extent of their failure to deliver.[20] Although, this idea of a developmental grant has its merits (encouraging institutions to develop a stronger research ethos), it is also a potential perverse incentive, in that institutes are rewarded more for doing less.

If the government determines the total of public funds that should be spent in a given year on higher education,[8] then in essence the total government funds available for research outputs is set in advance. Therefore as research outputs increase, the value of the unit declines. Hence, although the NFF recognises the budget constraints of the country (it is driven by the availability of public resources for funding higher education),[8] this formula is more likely to act as a disincentive than an incentive to increase research outputs.

In other words, given that the funds available for dispersal are finite, if all higher educational institutions increase their research outputs, then the monetary value of a research output unit will decline, a criticism which has been called the 'zero-sum game'.[21] Given that the basis of the NFF is to encourage future research output by means of rewards for past research outputs, a decrease in the monetary value of a research output unit is likely to create a disincentive to increase research outputs nationally.[21]

What constitutes an accredited journal?

Worldwide most institutions base their research outputs on publications in journals that are listed in the Institute for Scientific Information's (ISI) Science Citation Index, Social Sciences Citation Index and Arts and Humanities Citation Index.[3] In South Africa, publications in those journals listed in the above three ISI indices qualify for subsidy, and in addition, publications in journals listed in the International Bibliography of Social Sciences (IBSS) index, or in the Department of Higher Education and Training-approved South African journals list qualify for subsidy.

To be eligible for inclusion in the list of South African journals

accredited by the Department of Higher Education and Training, the purpose of the journal must be to disseminate research results, articles must be peer reviewed, journal contributions and distribution must be beyond a single institution, the journal must be published regularly, have an international standard serial number (ISSN) and have an editorial board. The Department of Higher Education and Training has also indicated that they plan to recognise three new journal databases for subsidy purposes in the future.

A pertinent issue is what constitutes a publication? For example, how are creative outputs such as artistic performances, paintings, concerts and novels recognised? Some higher educational institutions already have internal processes to take these outputs into account, although they are currently not recognised by the Department of Higher Education and Training. However, the Department of Higher Education and Training is at present wrestling with a procedure to recognise these outputs; hence this issue will not be discussed in this review. Further controversies, which are not discussed in this review, are what constitutes an accredited conference proceeding and the relative undervaluing of books and chapters in books within the South African subsidy formula.

Comparisons of the South African system to encourage research productivity with systems used in higher educational institutions in other countries in the world

The system in South Africa is perceived to be unique in that it is intended to provide direct financial reward to individual researchers for their outputs.[8,20] Although direct financial benefit to individuals may be intended, this is often not put into practice by the higher educational institutions, as will be discussed (see section titled 'Distribution of Department of Higher Education and Training research subsidy within higher educational institutions in South Africa').

In comparison, to South Africa's 'direct reward system', other countries have various different strategies aimed to stimulate research outputs. For example, in the United States of America, successful leverage of research support from the federal government is based on the assessment of an individual's research proposal, which incorporates details of his/her research track record.[2]

In the United Kingdom from 2014, obtaining government funding for research will be based on a system which places emphasis on an individual researcher's outputs and the citation of his/her publications (the Research Excellence Framework, REF).[4] The REF will replace the previous system used in the United Kingdom in the 1980s, 1990s and 2000s, namely the Research Assessment Exercise (RAE).[7] The RAE, which was used to determine the amount of funding provided by the government to individual institutions, was based upon the credentials of a limited number of the most prominent researchers in each academic department within an institution.[7]

The South African system is not actually that unique. In Australia, government funds granted for research are based on research income, publication counts and higher degrees completed.[3,5] Importantly, the Australian formula (similar to the South African NFF) is based solely on quantity, the impacts of which are discussed below in the section titled 'Positive and negative impacts of various approaches used to encourage research productivity'. As occurs in South Africa, whether the funding goes to the individual researcher or the institution appears to differ between the higher degree institutions in Australia.[3]

In Spain, individual researchers are rewarded on the basis of publications; however a financial bonus is only awarded for publications in high-impact factor journals.[6] A similar approach is used in Finland, except the institution rather than the individual researcher is the recipient of the financial benefits.[1] The merits of rewarding individuals as opposed to institutions are discussed under the section titled 'Financial reward of individuals versus institution'.

Positive and negative impacts of various approaches used to encourage research productivity

In order to encourage research productivity, a measure of research outputs is mandatory. The common issue that arises is whether research outputs should be measured purely by counting (termed research output audits) or whether an element of research quality (for example citations or journal impact factor) should be taken into account. This debate is far from resolved, however a commentary on the politics of publication, published in *Nature* in 2003,[9] incited a barrage of correspondence in which some interesting arguments both for,[6,10,11] and against[12-14] various measures of research productivity were raised.

Quantity versus quality

A number of criticisms have been raised regarding the potential negative impact of research output audits on research quality.[3,13] One of the major concerns is an encouragement of researchers to publish as many papers as possible (salami slicing)[14,22] and to preferentially choose to publish in those journals which have the least rigorous review process.[21]

Indeed, in South Africa, although there was a 50 to 60% increase in the number of publications produced by universities from 1990 to 1994 and 2004 to 2008;[23] only 57% of the publications that qualified for governmental subsidy in 2007 were published in internationally accredited journals.[23] Although this percentage has increased to 64% in 2008, 66% in 2009 and 69% in 2010, this increase is partly attributed to an increase in the number of South African journals listed in the ISI and IBSS.[24]

However, more convincing evidence of an increase in quantity at the expense of quality is provided by data from a study conducted on higher educational institutions in Australia.[3,13] In 1995, the formula by which the Australian government funds were distributed to higher educational institutions to support research activities was changed to incorporate publications.[3,13] Consequently, researchers could calculate the financial value of a publication [A$761 (R6 664.31) to A$1089 (R9 536.71) between 1995 and 2000].[13] As a consequence of increases in the total amounts to be distributed this value subsequently increased to A$3 000 (R26 271.94) in 2002.[13]

In her study, Butler[13] allocated all journals from the ISI's Science Citation Index into quartiles based on journal impacts calculated from five-year citation means. She then compared the Australian Universities' share of publications within these

quartiles prior to (1981–1985), with after (1996–2000) the incorporation of publications in the government formula. Although the share was stable within each quartile prior to the change in the funding formula, increases in the share occurred within each quartile after the change. However, of concern were the dramatically greater increases in the shares within the lower two quartiles (~100 and ~50%, respectively) compared to the increases in the shares in the higher two quartiles (only ~20% each).[13] Hence, although the change in the funding policy resulted in noticeable improvements in the total number of publication outputs (an increase of 25%) at a time when academic staff numbers were stable,[3] this increase was at the expense of quality.[3,13]

A study comparing the research outputs by two Australian universities lends further support to concerns of increased quantity at the expense of quality when rewards were based solely on the number of research outputs.[3] In this study, the research outputs in terms of quantity and quality of two Australian universities, which were using different systems to enhance research outputs, were compared. In the university that provided financial incentives based only on quantity, although research outputs increased, there was a simultaneous decline in publications in high-impact factor journals (a measure of research quality).[3] In the university that used a strategy in which the brightest young researchers were recruited and employed, the total number of publications increased as well as the number of publications in high-impact factor journals.[3] These studies clearly demonstrate the negative impact of rewards based solely on the counting of the number of publications.

In comparison to the Australian approach, in Spain a system in which only high-quality publications were rewarded was instituted in 1989.[6] To quote the Spanish parliamentary record, a bonus is awarded to individual researchers only for '…those articles of scientific worth in journals of recognized prestige in the field. …. In those disciplines for which international systems of quality of publications exist, reliance on these systems should be obligatory…'.[6]

Spanish research productivity doubled after the system of publication bonuses was passed into law.[6] Indeed, twice as many publications were produced between 1991 and 1998 compared to between 1982 and 1990, and the number of Spanish publications in ISI databases was increased.[6] These dramatic increments were not attributed to factors such as increased financial support, international collaboration or an increase in the number of staff.[25]

The consequences of this law were therefore that research productivity increased in both quantity and quality. Hence, the Spanish system of rewarding only high-quality publications appears to overcome the pitfalls of the Australian system, whereby rewarding research outputs irrespective of quality results in improved quantity at the expense of quality.

Further support of the use of a system based on rewarding researchers for publication in journals with a high impact factor was provided by Lomnicki[10] in his discussion on the positive impact of such systems on research productivity in Germany and France. Lomnicki[10] goes so far as to state that 'abandonment of objective methods of science evaluation derived from the SCI', would be most dangerous as 'it would remove a tool for rewarding researchers who attempt to do good science and for eliminating those who do not'.

A lesson to be learnt from these previous experiences, is that in order to avoid possible 'salami slicing' of research (data that should constitute one publication is divided into many smaller publications),[14,21,26] choosing in-house journals above international journals,[21,27] and preferences for choosing journals which are perceived to be easier to publish in,[21,26,27] the rewarding of research outputs as a means to encourage and enhance research outputs should be based on an assessment that includes the quality of publications.

The question therefore arises as to why high-quality publications are so important? The reason that some journals have higher impact is that they generate greater citations. In other words work published in higher impact journals is more highly cited than work published in lower impact journals. Hence, publications in high-quality journals are of greater value and have a superior impact on the scientific/research community.

However, the favouring of high-impact factor journals for the submission of manuscripts runs the risk of the journal choice becoming more important than the scientific message of the manuscript.[28] Indeed, it has been suggested that authors wishing to have their work published in the journal *Nature* claim novelty in their work, which is not entirely true, in order to enter into the review process.[12] During the course of the review such 'false novelty' is then identified and the manuscript is changed accordingly prior to publication.[12] However, the result is that work is published in *Nature* that is no more novel than that published in high-quality specialised journals.[12]

Nevertheless, there are other important benefits of sending manuscripts to high-impact factor journals.[11] Firstly, authors are more likely to receive meaningful feedback, as the top journals in each field are most likely to consult the top reviewers in the field. Secondly, the review process is generally more efficient from a time perspective, in that reviewers for top journals are generally given a maximum of 10 to 14 days to review a manuscript.

Collaboration

International collaboration between higher educational institutions is indeed recommended in that it enhances the citation and hence quality of research outputs.[3,29,30] However, collaboration creates a dilemma with regard to which individuals or higher educational institutions should be credited with research outputs generated by collaboration. If each country or institution involved is allocated a share of the collaborative publication (fractional counting) then the publication count will decrease.

Indeed, in a study of research outputs from Australian higher educational institutions, it was shown that collaboration resulted in a 17.8% reduction in the publication numbers for the period studied.[3] Moreover, as the average citations per publication were greater in those publications involving collaborators (5.53 vs 4.22), the total number of citations assigned to Australia decreased by 24.5% for the period studied.[3]

In the South African context, only those researchers affiliated to a South African higher educational institution are credited by the Department of Higher Education and Training. To translate this into research output units, below are some examples of the research output units generated by accredited journal publications with and without national or international collaborators:

- four authors all affiliated to one South African higher educational institution: $4 \times 0.25 = 1$ unit

- two authors affiliated to one South African higher educational institution and two authors affiliated to another South African higher educational institution: 2 × 0.25 = 0.5 unit to each South African higher educational institution.
- two authors affiliated to one South African higher educational institution and two authors affiliated to one non-South African higher educational institution: 2 × 0.25 = 0.5 unit to the South African higher educational institution.

Bearing in mind the above examples, it is clear that the NFF does not encourage collaboration with researchers who are not affiliated to a South African higher educational institution.[21,26]

Percentage public expenditure on higher education as a percentage of GDP and the financial value of research units

Over the past decade (2001–2009) the public expenditure on higher education as a percentage of GDP has increased in most countries [e.g. Argentina: 0.8% in 2001 to 0.9% in 2005 to 1.1% in 2009; Brazil: 0.7% in 2001 to 0.8% in 2005 to 0.8% in 2009; Finland: 1.6% in 2001 to 1.7% in 2005 to 1.8% in 2009; France: 0.9% in 2001 to 1.1% in 2005 to 1.2% in 2009; Ghana: 0.8% in 2001 to 1.1% in 2005 to 1.3% in 2009; Rwanda (values for 2001 not available): 0.6% in 2005 to 1.1% in 2009; Spain: 0.9% in 2001 to 0.9% in 2005 to 1.0% in 2009; New Zealand: 0.9% in 2001 to 0.9% in 2005 to 1.1% in 2009; USA: 0.9% in 2001 to 1.0% in 2005 to 1.0% in 2009],[17] although it has declined in some [Botswana (values for 2001 not available): 1.0% in 2005 to 0.9% in 2009; South Africa: 0.8% in 2001 to 0.8% in 2005 to 0.6% in 2009; United Kingdom: 0.8% in 2001 to 0.9% in 2005 to 0.4% in 2009].[17]

More specifically, in South Africa, the percentage of public expenditure on higher education as a percentage of GDP declined from 0.86% in 1987 to a value of 0.64% in 2008, with the greatest decline occurring between 1999 (0.80%) and 2002 (0.68%).[15] Although similar declines have occurred in other countries (Australia: 1.50% in 1974/75 to 0.89% in 1997/98 to 0.8% in 2009; United Kingdom: 0.8% in 2001 to 0.4% in 2009),[3,17] in South Africa the value of 0.74% in 2001 was well below the averages of 0.81% for a total of 84 countries worldwide; 0.85% for 15 other countries in Africa; 0.85% for six countries in South America; 0.88% for 13 countries in North America; and 0.95% for 21 countries in Europe.[15]

Moreover, the value in South Africa of 0.65% in 2007 was well below the percentages spent in sub-Saharan countries such as Botswana, Burundi, Ethiopia, Kenya, Lesotho, Ruanda, Senegal and Swaziland, where the values range up to 2.1% of GDP.[31] Although the percentages in South Africa were predicted to increase to 0.68% in 2008/9, 0.71% in 2009/10 and 0.74% in 2010/11,[20] the values recorded by UNESCO were 0.6% in 2007 and 0.6% 2009.[17]

The main impact of the decrease in government resources to higher educational institutions has been an increase in the number of students and an increase in tuition fees as a means of enhancing income generation.[15] In most circumstances the increase in student numbers has not been accompanied by an increase in staff numbers; hence resulting in increments in the student-to-staff ratios and a consequent decline in research productivity. Indeed in South Africa, the rise in student-to-staff ratios from 12.7 in 1986 to 18.0 in 2003[15] was accompanied by an ~15% decline in publications from 1997 to 2003.[15] In the historically advantaged institutions, the percentage decline in publications was even higher (20%).[15]

Comparable changes occurred at Australian universities when faced with a decrease in governmental financial support to higher education from 1.50% in 1974/75 to 0.89% in 1997/98.[3] The student-to-staff ratios rose from 12.81 in 1990 to 17.81 in 1999.[32] However, despite the increased demands placed on staff, the publication output increased by 25% over this time period.[3] The unexpected increment in publication output was primarily attributed to the introduction of a system to distribute funds to higher educational institutions in Australia based on publication outputs.[3] However, the negative impact of this system was a decline in the quality of the publications (see section titled 'Quantity versus quality').

Financial value of research outputs

Between 1987 and 2003, when the SAPSE formula was in use, the government subsidy awarded per publication unit was on average ~R22 000.[21] With the introduction of the NFF in 2005, the block grants awarded to higher educational institutions for research were stopped; hence resulting in ~R1.5 billion becoming available for rewarding research output on a competitive basis.[21] Consequently, the value of one research output unit rose from R77 606 in 2005 to R85 023 in 2007,[19,21] and then to R102 604 in 2009.[21] However, the value appears to have stabilised in more recent years, R110 000 in 2011[33] and currently R119 331, hence lending some credit to the criticism that the awarding of research funding using the NFF is a 'zero-sum' game.[21,22]

In comparison, in Australia the monetary value of a publication increased from A$761 (R6 664.31) to A$1 089 (R9 536.71) between 1995 and 2000.[13] Furthermore, as a consequence of increases in the total amounts to be distributed by government, this value subsequently increased to A$3 000 (R26 271.94) in 2002.[13] Other examples (obtained online) of the financial value of publications include:

- Qatar University: for publications in journals with an impact factor > 1.0, QR3 000 (R6 995.53) is awarded (40% to main author and 60% divided equally among co-authors including the main author) for each impact factor.
- University of South Pacific, Fiji: F$4 000 (R18 915.48) for A* (top) journals, F$3 000 (R14 186.61) for A journals, F$2000 (R9 457.74) for B journals and F$1 000 (R4 728.87) for C journals. The A, B, C, D ranking is according to the Australian Business Deans Council's rankings, which is used in preference to the journal impact factors in order to account for the variation in impact factors across disciplines. The awards are given as part of the researchers' salary and are taxed.
- Universities in Finland: FIM80 000 (R161 862.08) per impact factor is awarded to the institution rather than the individual.

Distribution of Department of Higher Education and Training research subsidy within higher educational institutions in South Africa

Financial reward of individuals versus institution

As the extent of governmental subsidy to higher educational institutions depends on the subsidy granted by the Department of Higher Education and Training for publications in accredited

journals, higher educational institutions encourage academics to publish in accredited journals. However, at most of the higher educational institutions, authors only receive a proportion of the total subsidy. In general, the higher educational institutions receive the major share of the funding, although this does differ between the different higher educational institutions (see section titled 'Different policies within and between South African institutions').

As discussed above, the policies also differ between higher educational institutions worldwide. For example, in Spain the individual researcher is the recipient of the rewards for research outputs,[6] whereas in Finland it is the institution and not the individual who benefits.[1] In Australia, similar to South Africa, the various higher educational institutions differ in the policies they have adopted.[3,13] Some have chosen to reward the individual researcher primarily, whereas at others the institutions are the major beneficiary.[3]

Different policies within and between South African institutions

What is provided below are some examples (those which are accessible) of the different policies adopted by the various higher educational institutions in order to distribute the subsidy block grants received from the Department of Higher Education and Training based on research outputs:

- Fifty per cent to faculty, of which 70% to individual researcher and 30% to faculty for publications in international journals, or of which 50% to researcher and 50% to faculty for publications in South African journals.
- Proportion of university research budget is distributed to each faculty based on the units produced by each of these faculties. Each faculty individual research committee decides on the disbursement to the schools. Schools then decide whether to distribute to departments, divisions and/or individual researchers. It is clearly stipulated that these funds may only be used for research-related or academic activities and that the funds may not be used to supplement salaries.
- Sixty per cent to the individual researcher, 15% to faculty or department, 15% to research office, 10% to vice chancellor's office. It is clearly stipulated that these funds can only be used for research and research-related activities. No cash payments are made to individual researchers.
- The university research committee allocates to each faculty a proportion of the funds received in the annual block grant. The proportion awarded to each faculty is based on a formula which considers the accredited outputs of each faculty and the throughput of postgraduate students, and includes recognition of outputs from the arts (such as design, compositions, exhibitions and performances).
- One higher educational institution incentivises researchers by rewarding top researchers with annual research awards of up to R500 000. The recipients of these awards are allowed to keep half for personal use, but have to use the rest for their research. However, the exact source of funding for these research awards is not clear.

Conclusions and proposals

As government policies on research funding of institutions have a direct impact on the behavior of academics with regard to research outputs, there is a need to refine these policies in order to produce the desired academic behaviours. To avoid the possibility of producing quantity at the expense of quality, an element of quality needs to be incorporated into the policy. A proposal, based on the Spanish system, would be to incorporate a higher weighting for publications in higher impact factor and/or rank in discipline journals. It is probable that such a system would also address the disincentive provided by the current formula, to collaborate internationally (as international collaboration generally results in increased quality of publications).

In addition, the potential perverse incentive created by the awarding of developmental grants to underperforming institutions could be minimised by substantially reducing the monetary value of the developmental grants. Moreover, developmental grants should not be awarded on a continual basis. In other words, an institution that receives a developmental grant has to show substantial annual improvements in order to warrant further developmental grants.

A bolder proposal, which would support the curtailment of developmental grants, is that more funds should be given to those higher educational institutions where most of the publications are produced, in order to ensure that more research will be done at these institutions. Many believe that a greater incentive to individuals would be provided if a larger proportion (although probably not all) of the subsidy earned was granted to the individual(s) who generated the subsidy. However, these funds should be used for research purposes and not for the supplementation of salaries (bearing in mind the tax implications). Importantly, a way forward is to take heed of the evidence provided and thereby avoid the mistakes made by some, and follow the successful examples of others.

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Cardiovascular Topics

Comparison of the effects of gelatin, Ringer's solution and a modern hydroxyl ethyl starch solution after coronary artery bypass graft surgery

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Abstract

Objective: **The aim of this study was to compare the effect of 6% hydroxyl ethyl starch solution with 4% gelatin and Ringer's solutions on the haemodynamic stability of patients after coronary artery bypass graft (CABG) surgery and immediately after discontinuation of cardiopulmonary bypass (CPB).**

Methods: **This was a randomised, double-blind clinical trial of 92 patients who were candidates for on-pump CABG. After discontinuation of CPB, all patients were transferred to the intensive care unit (ICU) and divided randomly into three groups. The first group received Ringer's solution, the second group 4% gelatin, and the third 6% hydroxyl ethyl starch (HES) solution (Voluven). Haemodynamic parameters such as heart rate, mean arterial pressure, systolic blood pressure, diastolic blood pressure, central venous pressure, cardiac output and the presence of arrhythmias were documented.**

Results: **The volume needed for maintaining normal blood pressure and central venous pressure in the range of 10–14 mmHg was less in the HES group than in the other groups. The volume was similar however in the gelatin and Ringer's groups in the first 24 hours after surgery. Urinary output in the first four and 24 hours after surgery were significantly higher in the HES group than in the other two groups. Mean creatinine levels were significantly lower in the HES group.**

Conclusion: **HES (6%) had a better volume-expanding effect than gelatin (4%) and Ringer's solutions, and its short-term effects on renal function were also better than gelatin and Ringer's solutions.**

Keywords: CABG, haemodynamic stability

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Immediately after coronary artery bypass graft (CABG) surgery, patients are haemodynamically unstable and need fluid support.[1] The purpose of using volume expanders after cardiac bypass surgery is to maintain stable haemodynamics.[2] Applying an appropriate fluid with enough volume at this stage may prevent systemic hypoperfusion and cellular hypoxia, which lead to systemic lactic acidosis.[3] Furthermore, after cardiopulmonary bypass patients experience systemic inflammatory responses and endothelial damage, which lead to fluid extravasations and interstitial oedema. Therefore correct volume administration is recommended in this situation.[4]

There is controversy regarding the different types of solutions used after CABG, and various researchers have used materials such as crystalloid solutions or colloids, including albumin and gelatin, or other agents such as hydroxyl ethyl starch solutions. Volume expansion is an important aspect of these solutions, however, side effects, such as inflammatory responses, and effects on endothelial integrity and on organs such as the kidney should also be considered during their administration.[4]

Gelatins are polydispersed polypeptides produced by degradation of bovine collagen. Three types of modified gelatin products are now available: cross-linked or oxypolygelatins (e.g. Gelofundiol®), urea cross-linked (e.g. Haemacel®) and succinylated or modified fluid gelatins (e.g. Gelofusine®). Their molecular weight (MW) ranges from 5 000–50 000 Da, with an average of 30 000–35 000 Da. The various gelatin solutions have comparable volume-expanding powers and all are said to be safe with regard to coagulation and organ function (including kidney function).[2]

Hydroxyl ethyl starch (HES) is a widely used plasma substitute for correcting hypovolaemia in cardiac surgery patients. HES preparations vary with regard to concentration, mean MW, molar concentration, C_2:C_2 ratio, and solvent. HES solutions with a low MW and a low molar concentration are thought to be safe with regard to coagulation, and increased bleeding tendency no longer appears to be a problem (Valoven, HES 6%), even when higher doses are given.[3]

Some authors believe that albumin has a better volume-expanding effect than HES.[5] Rehm *et al.* have shown that HES and albumin solutions caused mild systemic acidosis in patients undergoing normovolaemic haemodilution after cardiac surgery.[6] Others maintain that a short time of infusion of a rapidly degradable HES solution after cardiac surgery produces impairment in fibrin formation and clot strength in thrombo-elastometry tracings. In this clinical setting, human albumin does

not impair homeostasis.[7]

Correcting hypovolaemia with HES has been suggested to be associated with an increased risk of acute renal failure, and interest has recently been focused on the influence of HES solutions on renal function.[8] Boldt *et al.* found better kidney function and less inflammation with the use of HES than with albumin solutions.[4]

The aim of this study was to compare the effect of 6% hydroxyl ethyl starch solution with 4% gelatin and Ringer's solutions on haemodynamic stability of patients after CABG surgery and immediately after discontinuation of cardiopulmonary bypass.

Methods

This was a prospective, randomised, double-blind clinical trial in 92 patients who were candidates for on-pump CABG. The age range of patients was from 40 to 75 years. Exclusion criteria were left ventricular ejection fraction < 40%, right heart failure, emergency patients, pump time > 180 minutes and clamp time > 90 minutes, patients who needed re-operation within the first six hours due to surgical haemorrhage or other reasons, renal failure needing haemodialysis, and those with respiratory failure.

All patients received pre-anesthesia medication. Lorazepam (1 mg orally) was given the night before the operation and intramuscular morphine (0.1 mg/kg) one hour before induction of anaesthesia in all patients. In the operating room, lidocaine (1%) was used for access to arterial and peripheral vessels and Ringer's crystal solution was administered in a dose of 5–10 ml/kg. Anaesthesia induction was started with intravenous medazolam sufentanyl and pancranium.

After the use of 100% oxygen by mask, patients were intubated with an endotracheal tube and connected to a mechanical ventilator and central venous pressure (CVP) was introduced in the right internal jugular vein. Maintenance of anaesthesia was achieved with continuous infusion of idazolam, atrocurium and sufentanyl. After infusion of 300 IU/ kg heparin, the patient went on-pump and the activated clotting time (ACT) was above 480 s, mean arterial pressure 60–70 mmHg, haematocrit level was 22–27%, and the temperature was set at 32°C.

After discontinuation of cardiopulmonary bypass (CPB) all patients were transferred to the intensive care unit (ICU) and were randomly divided into three groups. The first group received Ringer's solution, the second gelatin (4%), and the third group hydroxyl ethyl starch solution (HES) (6%) (Voluven) as a volume expander to maintain the CVP between 7 and 14 mmHg. Packed cells were infused where the haemoglobin level was lower than 8 mg/dl and fresh frozen plasma (FFP) was used for continuous bleeding with a normal range of ACT and APTT (activated partial thromboplastin time).

Cardiac output was monitored with a NICO instrument and haemodynamic values were monitored continuously. In situations where, after maintaining adequate volume, the mean arterial pressure was below 60 mmHg and cardiac index below 2 l/min/m^2 body surface area, inotrope infusion (dobutamine or epinephrine) was started.

Haemodynamic parameters such as heart rate, mean arterial

TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF PATIENTS (± SD)

	Ringer's solution (n = *29*)	*Gelatin (4%)* (n = *31*)	*HES (6%)* (n = *32*)	p-*value*
Age (year)	59 (11)	60 (8.7)	57 (10.4)	0.495
Weight (kg)	73.4 (10.8)	72.5 (11.9)	74.4 (11)	0.795
Height (cm)	167.4 (8.2)	165 (8.3)	167 (6.7)	0.750
Ejection fraction %	41 (8.4)	45 (6.7)	46 (5.9)	0.195
Numbers of bypass	3 (0.3)	3 (0.4)	2.9 (0.4)	0.449
Drug usage:				
Plavix	1	4	0	0.283
Beta-blocker	26	22	21	0.78
ASA	17	19	18	0.410
ACE inhibitors	15	16	17	0.380
Nitrates	14	12	13	0.210
Oral antidiabetic agents	7	8	7	0.150
Other antihypertensive agents	5	6	5	0.110
Diuretics	13	11	12	0.225
Anesthesia time (min)	263 (191–310)	250 (181–301)	247 (185–305)	0.140
CPB time (min)	109 (37)	99 (28)	106 (34)	0.120
Cross-clamp time (min)	63 (26)	55 (20)	59 (25)	0.170
Systolic BP (mmHg)	120 (11)	123 (16)	114 (9)	0.211
Diastolic BP (mmHg)	75 (11)	73 (10)	70 (9)	0.293
Na (meq)	134 (7)	140 (9)	135 (20)	0.212
K (meq)	4.3 (0.44)	4.3 (0.47)	4.35 (0.45)	0.143
PTT (s)	30 (4.5)	35 (5.3)	29 (5)	0.136
INR	1.1 (0.25)	1.08 (0.2)	1.08 (0.16)	0.278
Haemoglobin (g/dl)	12.7 (8.1–15)	12 (9–14)	12.3 (8.4–13.5)	0.323
BUN (g/dl)	13 (9–23)	15 (9–31)	15.5 (9–23)	0.275
Creatinine (g/dl)	0.9 (0.7–1.04)	0.95 (0.5–1.3)	1(0.7–1)	0.340

CBP: cardiopulmonary bypass, BP: blood pressure, ACE: angiotensin converting enzyme, PTT: partial thromboplastin time.

TABLE 2. COMPARISON OF DETERMINED VARIABLES BETWEEN THE THREE GROUPS (± SD)

	Ringer's solution	*Gelatin (4%)*	*HES (6%)*	p-*value*
MAP after pump	61 (4)	63 (4)	64 (4)	0.410
MAP after moving to ICU	62 (3)	61 (3)	63 (4)	0.380
MAP after 2 hours in ICU	64 (4)	67 (3)	68 (4)	0.395
MAP after 4 hours in ICU	67 (5)	69 (6)	71 (7)	0.295
MAP after 6 hours in ICU	69 (5)	73 (4)	74 (7)	0.220
MAP after 12 hours in ICU	74 (9)	73 (11)	75 (10)	0.345
MAP after 24 hours in ICU	73 (7)	71 (4)	75 (5)	0.275
HR after moving to ICU	62 (3)	64 (5)	68 (6)	0.175
HR after 2 hours in ICU	73 (7)	74 (5)	72 (4)	0.195
HR after 4 hours in ICU	77 (7)	81 (6)	78 (5)	0.170
HR after 6 hours in ICU	75 (7)	80 (6)	78 (6)	0.220
HR after 12 hours in ICU	77 (7)	79 (5)	80 (6)	0.230
CVP after pump	11 (10–14)	12 (10–14)	12 (10–14)	0.270
CVP after moving to ICU	12 (10–14)	11 (10–14)	13 (10–14)	0.215
CVP after 2 hours in ICU	13 (10–14)	12 (10–14)	11 (10–14)	0.179

MAP: mean arterial pressure, HR: heart rate, CVP: central venous pressure

pressure, systolic blood pressure, diastolic blood pressure, central venous pressure, cardiac index and the presence of arrhythmias were documented. Other independent variables such as urinary output, serum electrolytes and serum creatinine levels were measured immediately after discontinuation of CPB, before transferring the patient to the ICU, immediately after arriving in ICU, and after two, four, six, 12 and 24 hours in ICU.

Study approval was obtained from the ethics committee of our Centre and written informed consent was obtained from the patients. The data were put into spreadsheets and comparison of variables between groups was done using Chi-squared or ANOVA tests.

Results

Biometric data were similar in all groups. Mean anaesthesia time, pump time and cross-clamp time were the same in all three groups (Table 1). There were no mortalities in any of the groups. There were no significant differences in systolic and diastolic blood pressure between the three groups, and haemoglobin, blood urea nitrogen (BUN), creatinine, Na and K levels, partial thromboplastin time (PTT), and international normalised ratio (INR) were same in the three groups. No case was excluded from this survey and no significant differences were found between groups for mean arterial pressure, central venous pressure and heart rate (Table 2).

The volume needed for maintaining normal blood pressure and central venous pressure in the range of 7–14 mmHg was less in the HES group than in the other groups, but similar in the gelatin and Ringer's groups in the first 24 hours after surgery. Urinary output in the first four and 24 hours after surgery was significantly higher in the HES group than in the other two groups.

Mean creatinine levels on the first day post operation were 1.25 ± 0.23 mg/dl in the Ringer's group, 1.3 ± 0.24 mg/dl in gelatin group and 1.06 ± 0.13 mg/dl in the HES group. On the second day post operation, these values were 1.4 ± 0.25, 1.41 ± 0.26, 1.13 ± 0.16 mg/dl in the Ringer, gelatin and HES group, respectively. Mean creatinine levels were significantly lower in the HES group (Table 3).

TABLE 3. COMPARISON OF DETERMINED VARIABLES BETWEEN THE THREE GROUPS (± SD)

	Ringer's solution	*Gelatin (4%)*	*HES (6%)*	p-*value*
Mean volume infused during surgery (ml)	2150 (340)	1925 (290)	1320 (250)	0.011
Mean volume infused in first 24 hours in ICU (ml)	6100 (400)	5300 (380)	3500 (210)	0.001
Units of packed cells infused in 24 hours in ICU	94	93	96	0.275
Units of FFP infused in 24 hours in ICU	53	53	48	0.170
Units of platelets infused in 24 hours in ICU	28	34	23	0.145
Amount of haemorrhage in first 24 hours (ml)	1300 (260)	1350 (270)	1280 (280)	0.170
Amount of urine output in first 4 hours in ICU (ml)	1700 (180)	1760 (190)	2250 (290)	(0.02)
Amount of urine output in first 24 hours in ICU (ml)	4450 (310)	4520 (340)	5200 (330)	(0.03)
Creatinine in first postoperative day (mg/dl)	1.32 (0.23)	1.31 (0.24)	1.06 (0.13)	0.004
Creatinine in second postoperative day (mg/dl)	1.4 (0.25)	1.41 (0.26)	1.13 (0.16)	0.004

There were no significant differences between the three groups in the amount of blood, FFP and platelet transfusions in the ICU (Table 3). Arrhythmias in ICU, extubation time and ICU stay were the same in all groups (Table 4).

Discussion

The main result of this study was that haemodynamic stability could be achieved after CABG surgery with less volume of HES than gelatin and Ringer's solutions. The kidney function was better in the short term in the HES group than in the other two groups.

In our centre, we selected adult patients for CABG. We are aware that enough of a suitable volume expander is needed for haemodynamic stability after CABG, and that some volume expanders have side effects. Patients usually have a systemic inflammatory response after CPB for CABG and the resultant endothelial damage leads to hyperpermeability and interstitial oedema.[4]

Some researchers have shown that HES reduced inflammation and endothelial damage.[4] It also maintained the cell's integrity and function.[4,9] Lower-molecular weight HES molecules had an effect on the arteriolar integrity and could reduce arteriole-induced oedema in clinical and experimental models.[10] Reported effects of HES usage were improvement in the microcirculation

TABLE 4. COMPARISON OF DETERMINED VARIABLES BETWEEN THE THREE STUDIED GROUPS (± SD)

	Ringer's solution	*Gelatin (4%)*	*HES (6%)*	p-*value*
Extubation time (min)	452 (418–508)	445 (410–500)	463 (420–430)	0.215
ICU stay time (hours)	46 (42–48)	47 (43–48)	45 (42–48)	0.175
Arrhythmias in ICU (n)	2	0	2	0.459

and the oxygenation of organs.[11] HES also had an effect on inflammation. Reduction of macrophage inflammatory protein (MIP-2), IL-1β and TNF-α levels was found to be a mechanism for reduction of inflammation after the use of HES.[12]

The most dangerous complication after CABG is kidney damage and some researchers demonstrated kidney damage after the use of HES but found gelatin (4%) to be safer.[8] Others have shown little reduction in glomerular filtration rate (GFR) after the use of high-molecular weight HES.[13] Boldt *et al. r*eported a lower inflammation rate and better GFR with HES.[4]

In our study there was better haemodynamic stability with lower volumes of HES. Renal function was good after its use in the first two days after CABG, which indicates that renal function can be maintained after use of 6% HES. Other reporters have shown less renal damage after the use of HES than with gelatin, albumin and Ringer's solutions.[4]

In our study we used less volumes of HES than Ringer's solution and gelatin and this produced a better volume-expanding effect with HES than with gelatin and Ringer's solutions. Better oxygenation and lower serum lactate concentration were shown after the use of HES than with gelatin.[15] There were no differences between the three groups as far as mortality rate is concerned.

There were some limitations to the study. Because of the systemic inflammatory response after CPB, it would have been advisable to compare inflammatory biomarkers in the three groups but this was not done. It has been reported that HES had an effect on the acid–base balance in some studies, but this was not determined in our study.

Conclusion

Our study showed that HES (6%) had a better volume-expanding effect than gelatin (4%) and Ringer's solution, and its short-term effects on renal function were also better than with gelatin and Ringer's solution.

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Cardiac surgical experience in northern Nigeria

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Abstract

A pilot study was undertaken to determine the feasibility of establishing a heart surgery programme in northern Nigeria. During three medical missions by a visiting US team, in partnership with local physicians, 18 patients with heart diseases underwent surgery at two referral hospitals in the region. Sixteen (88.9%) patients underwent the planned operative procedure with an observed 30-day mortality of 12.5% (2/16) and 0% morbidity. Late complications were anticoagulant related in mechanical heart valve patients and included a first-trimester abortion one year postoperatively, and a death at two years from haemorrhage during pregnancy. This has prompted us to now consider bioprosthetics as the valve of choice in women of childbearing age in this patient population. This preliminary result has further stimulated the interest of all stakeholders on the urgency to establish open-heart surgery as part of the armamentarium to combat the ravages of heart diseases in northern Nigeria.

Keywords: rheumatic, congenital, heart surgery

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Northern Nigeria, with over 50% of the nation's estimated 150 million population, has several tertiary-care hospitals but none has the capacity for open-heart surgery to service the large number of indigent patients affected by the ravages of rheumatic and congenital heart diseases. These patients therefore have a grim prognosis and many face untimely death, with the exception of a minority who have the financial resources or are able to obtain government or private sponsorship to travel abroad for the recommended surgical treatment.

Medical treatment is the only available option and is often palliative, with many patients requiring frequent hospitalisations for congestive heart failure and with a resultant poor quality of life. Because of this dismal outlook, the Global Eagle Foundation, a US-based non-governmental organisation, in partnership with the Nigerian Government, decided to undertake a pilot project on the feasibility of establishing a heart programme to fill this void and bring hope to these patients.

This report summarises our initial experience with the first series of open-heart surgeries ever performed in northern Nigeria.

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Methods

Between October 2006 and April 2008, patients referred with heart diseases to the Cardiology Division of the National Hospital, Abuja and Ahmadu Bello University Teaching Hospital, Zaria, were screened and potential surgical candidates were shortlisted. After further evaluation, patients testing positive for HIV/AIDS and hepatitis B and C were excluded. Due to the limited resources, the more symptomatic patients were selected to undergo surgery.

Diagnosis was established non-invasively through clinical examination and confirmed by transthoracic echocardiogram (TTE). Transoesophageal echocardiogram (TEE) and cardiac catheterisation were not available then at either institution. All the valvular patients met the American College of Cardiology/American Heart Association (ACC/AHA) class I indications for surgery.

During the three missions, each lasting about one week, 18 patients comprising 12 (66.7%) females and six (33.3%) males, with age range five to 42 years (mean 17.6 years), underwent heart surgery. Twelve (66.6%) patients had acquired heart diseases, predominantly rheumatic valvular disease and six (33.3%) had congenital heart disease, of whom 55.5% (10/18) were either in NYHA class 3 or 4 pre-operatively (Table 1).

The EURO score was used for risk stratification in the valve patients, with a mean score of 5.51, and range of 3.13–12.04. Invasive monitoring was by arterial and central venous pressure lines, with a swan ganz catheter and cardiac output measurements used sparingly due to limited supply.

Surgical exposure was through a median sternotomy for patients requiring the heart–lung machine. Cardiopulmonary bypass was via ascending aortic and atrial–bicaval cannulations. Moderate systemic hypothermia at 30°C was used in all patients and myocardial protection during aortic cross clamping was by cold-blood cardioplegia administered antegrade, retrograde or both.

Standard blood-conservation techniques used included, whenever possible, retrograde priming of the pump with removal of blood and cell saver. Two patients received low-dose aprotonin. The blood banks did not have the capability to provide component blood therapy and therefore only whole blood was available to transfuse for either anaemia or coagulopathy. Postoperative follow up was by clinic visits or telephone calls and was completed in 87.5% of surviving patients.

Results

Of the 18 patients undergoing surgery, 16 (88.8%) completed the planned operative procedure. Two patients were deemed inoperable after sternotomy due to supra-systemic pulmonary

TABLE 1. PRE-OPERATIVE DIAGNOSIS AND NYHA CLASS

Diagnosis	*Number of patients*
Acquired heart disease	
Severe mitral regurgitation	7
Severe mitral stenosis	2
Severe aortic regurgitation	2
Penetrating heart wound	1
Congenital heart disease	
Ventricular septal defect	2
Patent ductus arteriosus	2
Atrial septal defect	1
Tetralogy of Fallot	1
NYHA	
Class I	1
Class II	7
Class III	3
Class IV	7

hypertension, determined by direct-needle transducer measurements. There was no pre-operative swan ganz floated in these two patients as none was available, and the pre-operative TTE had grossly underestimated the pulmonary artery pressures. The operative procedures performed are listed in Table 2.

Time on cardiopulmonary bypass was 20–205 minutes (mean 130) and on aortic cross clamp 89–114 minutes (mean 103). All patients were initially easily weaned off bypass, although two later required intra-aortic balloon pump (IABP) post bypass for haemodynamic instability. Mechanical valves were used for heart valve replacement and comprised four St Judes, three ATS and two On-X valves. Septal defects were closed primarily if less than 1 cm in diameter or otherwise glutaraldehyde-treated autologous pericardium was used. An 8-mm Gore-Tex graft was used for the modified Blalock-Taussig shunt.

Seven patients (43.7%) required blood, with a mean of two units of whole blood transfused. Two patients who received aprotonin were almost bone dry and required no transfusion. All patients were extubated within 12 hours, with the exception of one patient who required ventilation for longer than 24 hours. Anticoagulation with intravenous heparin and Coumadin was started on postoperative day 2 if there was no evidence of significant bleeding. Heparin was discontinued once the INR was within the desired therapeutic range of 2.5 to 3.5.

Thirty-day operative mortality was 12.5% (2/16) and involved the first index cases at both institutions to undergo open-heart surgery. Both were females with chronic severe aortic regurgitation from rheumatic heart disease. The first patient had severe pericarditis with dense adhesions, and following uneventful surgery developed sudden pulmonary hypertension and systemic hypotension a few minutes after protamine sulphate administration, which was unresponsive to standard therapeutic measures. Heparin was re-administered and cardiopulmonary bypass quickly reinstituted due to haemodynamic collapse. After a period of rest with an empty, beating heart, the patient was separated from the bypass with inotropes and IABP. She developed coagulopathy and died of haemorrhage, as fresh frozen plasma, platelets and cryoprecipitate were unavailable at the blood bank.

The second patient, also after an uneventful surgery, developed unexplained sudden hypotension while transferring

TABLE 2. OPERATIONS PERFORMED

Operations	*No of patients*
Acquired heart disease	
Mitral valve replacement	7
Aortic valve replacement	2
Repair right ventricular laceration	1
Congenital heart disease	
Closure ventricular septal defect	2
Ligation patent ductus arteriosus	2
Closure atrial septal defect	1
Modified Blalock-Tausig shunt	1

to the intensive care unit and required pressors and IABP for stabilisation. She required prolonged ventilation and died four days later from pneumonia-related sepsis due to unavailability of potent broad-spectrum antibiotics, in addition to a delay in obtaining microbiological laboratory results.

There was no re-operation for bleeding, cardiac tamponade or valvular dysfunction. There was no stroke, renal failure, deep sternal wound infection or any other major morbidity. At follow up there was one anticoagulant-related morbidity one year postoperatively in a valve patient on Coumadin, resulting in a first-trimester abortion, and a late mortality two years postoperatively in the same patient from anticoagulant-related haemorrhage during another pregnancy.

Discussion

In the 50 years since the introduction of the heart–lung machine to clinical practice by Gibbons in 1953, open-heart surgery has matured as a speciality and become routine in all the developed nations and most of the underdeveloped world. However, sub-Saharan Africa which, according to the World Health Organisation lags behind in most aspects of healthcare, has yet to develop heart surgery programmes to any significant extent. While infectious diseases and malnutrition presently remain their leading public health concerns, cardiovascular diseases are expected to gain more prominence in coming decades.

Although there is a paucity of data on heart diseases in sub-Saharan Africa, the consensus of experts is that rheumatic fever and the sequelae of rheumatic heart disease are the commonest forms of heart disease in Africa, followed closely by dilated cardiomyopathy.[1-3] Both of these diseases affect mainly children and young adults from socio-economically disadvantaged segments of the population living in unsanitary conditions, which predisposes them to infectious diseases such as Group A Streptococcal pharyngitis, compounded by malnutrition as a consequence of poverty.

While the exact incidence of congenital heart disease in the population is unknown, it is estimated to occur in one in 100 live births worldwide. Ischaemic heart disease, prevalent in the industrialised world, is rare in sub-Saharan Africa and seen only in the small segment of the population exposed to Western diet and lifestyles.

Seventy per cent of the estimated 150 million population of Nigeria live below the poverty line, with inadequate housing, sanitation and basic health services; 45.1% of the population is under 15 and 4.8% over 65 years of age, with a life expectancy of 52 years for men and 52.2 years for women.[4] It is therefore

obvious that the number of children and young adults from socio-economically disadvantaged backgrounds exposed to rheumatic fever and the sequelae of rheumatic heart disease is enormous.

Moreover, the incidence is expected to increase in coming decades due to worsening economic conditions in sub-Saharan Africa, combined with the ravages of HIV/AIDS, rendering many children orphans and homeless. Because of lack of heart surgery programmes in most of sub-Saharan Africa, many of these patients with heart diseases and requiring surgery are therefore treated only medically due to the prohibitive cost of travelling abroad for open-heart surgery.

In Nigeria, the first open-heart surgery was performed at the University of Nigeria Teaching Hospital, Enugu (UNTH) in 1974 by a team from the United Kingdom, led by Prof Magdi Yacoub.[5] The hospital, for years the only cardiac surgery centre in Nigeria, has however remained dormant in recent years.[6] A second heart programme, also in southern Nigeria, started at the Lagos State University Teaching Hospital, Lagos (LASUTH) in 2004 and is still in its infancy.

In contrast, northern Nigeria with over 50% of the country's population has no heart surgery programme, despite the large number of patients needing such specialised services. As a result, many of the patients referred to us for surgery had advanced cardiomyopathy with pulmonary hypertension and cardiac cachexia.

One might have expected a higher mortality and morbidity in this pilot study because of the high risk profiles, coupled with the total lack of experience at institutional and personnel levels. However, the results were satisfactory, as the two deaths were potentially avoidable and attributable to lack of needed resources from the blood bank and pharmacy. The observed mortality in this high-risk group was exaggerated by our relatively low numbers. There was of course an obvious learning curve with our index cases, involving all the support services and personnel, which prevented further complications in subsequent patients at both institutions.

Identified deficiencies included lack of blood bank capability to provide component blood therapy, which contributed to the death of our first patient from severe coagulopathy, and the unavailability of potent broad-spectrum antibiotics from the pharmacy, contributing to the second mortality from nosocomial infection. Furthermore upon realising the total absence of respiratory therapist support and the less-than-ideal sterility of the ventilatory tubing which was reused for multiple patients, all efforts were made for early extubation within a few hours of surgery to reduce the risk of cross contamination of the respiratory tract.

This strategy required coordination by the anesthesiologists and perfusionist, with the use of easily reversible anaesthetic agents and keeping patients dry with ultrafiltration on bypass to reduce lung water which might affect lung compliance postoperatively. We believe that this strategy of early extubation and mobilisation, along with the relatively young age of the patients may have contributed to the absence of any major morbidity in the surviving patients.

The late morbidity and mortality at one and two years, respectively, were both anticoagulant-related haemorrhage, in a pregnant woman with a mechanical valve, and poor compliance with Coumadin monitoring. Because of the higher risk of valve calcification in the young and the cost of a possible future re-operation for structural valve deterioration, all the patients had opted for a mechanical valve, although some were already on anticoagulation for chronic atrial fibrillation.

The risk of thromboembolism and haemorrhage is estimated at about 2% per year, even in the best setting, and this figure is likely to be even higher in our impoverished population with inadequate anticoagulation monitoring. The cumulative risk for thromboembolic and haemorrhagic complications in these patients over a lifetime is therefore enormous and has prompted us to reconsider the use of mechanical valve replacement in this largely poor and uneducated population, most especially in females of childbearing age. This is particularly important as rheumatic heart disease in northern Nigeria appears more common in females, as reported by Danbauchi *et al*.[3] We therefore now recommend bioprosthetic valves to females of childbearing age in this patient population.

Because of poverty and lack of education, monitoring of adequate levels of anticoagulation can be challenging, if not impossible, especially for those living in remote villages that are unable to follow up regularly at the clinics. Due to lack of standardisation and quality control, the results, even in those undergoing regular monitoring, are sometimes unreliable and inconsistent, perhaps due to the use of expired reagents in some of the laboratories.

Conclusion

Despite the fact that most of the patients had advanced cardiomyopathy and were often malnourished, the overall outcome was excellent considering that this was the first series of heart surgeries in this region, performed in less-than-ideal operating conditions, including lack of equipment and ancillary support services. The two operative mortalities were potentially avoidable had adequate support structures been in place, and also represented a learning curve for this type of delicate surgery at both institutions. These initial results are however encouraging and show that with adequate government financial support for equipment acquisition and human capacity building, northern Nigeria should be able to support two heart surgery programmes to service this large patient population.

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Increased relative wall thickness is a marker of subclinical cardiac target-organ damage in African diabetic patients

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Abstract

Objective: **To assess the prevalence and covariates of abnormal left ventricular (LV) geometry in diabetic outpatients attending Muhimbili National Hospital in Dar es Salaam, Tanzania.**

Methods: **Echocardiography was performed in 61 type 1 and 123 type 2 diabetes patients. LV hypertrophy was taken as LV mass/height$^{2.7}$ > 49.2 g/m$^{2.7}$ in men and > 46.7 g/m$^{2.7}$ in women. Relative wall thickness (RWT) was calculated as the ratio of LV posterior wall thickness to end-diastolic radius and considered increased if ≥ 0.43. LV geometry was defined from LV mass index and RWT in combination.**

Results: **The most common abnormal LV geometries were concentric remodelling in type 1 (30%) and concentric hypertrophy in type 2 (36.7%) diabetes patients. Overall, increased RWT was present in 58% of the patients. In multivariate analyses, higher RWT was independently associated with hypertension, longer isovolumic relaxation time, lower stress-corrected midwall shortening and circumferential end-systolic stress, both in type 1 (multiple $R^2 = 0.73$) and type 2 diabetes patients (multiple $R^2 = 0.66$), both $p < 0.001$. These associations were independent of gender, LV hypertrophy or renal dysfunction.**

Conclusion: **Increased RWT is common among diabetic sub-Saharan Africans and is associated with hypertension and LV dysfunction.**

Keywords: left ventricular geometry, African diabetes, relative wall thickness

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The co-existence of diabetes with other cardiovascular risk factors, such as hypertension and obesity, may contribute to the association of diabetes with subclinical cardiac target-organ damage such as left ventricular (LV) hypertrophy and dysfunction. In addition, several reports have suggested that diabetes has direct adverse effects on the heart, independent of obstructive coronary artery disease.[1,2] In the Strong Heart study, non-insulin dependent diabetes was associated with a 12 to 14% higher LV mass/height$^{2.7}$ as well as reduced LV systolic function and increased arterial stiffness.[3] Among hypertensive diabetic African Americans, increased relative wall thickness (RWT) and LV hypertrophy have been found to be more prevalent,[4,5] and earlier development of cardiac end-organ damage than in Caucasians has been suggested.[6]

In sub-Saharan Africa, diabetes and other cardiovascular diseases were considered rare.[7] As a result, research focus has been on infectious diseases. However, recent publications in the region have shown an increase in the prevalence of diabetes, hypertension and other cardiovascular risk factors,[8] and a high prevalence of LV hypertrophy, in particular in hypertensive patients, has been reported.[9] However, there are limited data on subclinical cardiac target-organ damage in diabetic patients.

The aim of the present study was therefore to determine the prevalence and covariates of abnormal LV geometry among type 1 and type 2 diabetes outpatients of African origin attending Muhimbili National Hospital in Dar es Salaam, Tanzania.

Methods

This study was a prospectively planned follow-up examination of 244 diabetic patients of African origin who participated in a diabetes study programme that included clinical and biochemical examination at Muhimbili National Hospital in Dar es Salaam, Tanzania in 2003–2004.[10,11] Of the total 244 patients who participated in the first survey, 184 patients (75%) were still receiving care at the diabetes outpatient clinic in Muhimbili National Hospital in 2008. Patients were informed about the follow-up study when attending their regular visits at the diabetes outpatient clinic and subsequently invited to participate. All 184 patients agreed to participate and signed informed consent.

A structured questionnaire was used for interviewing the patients on socio-demographic characteristics, history of other cardiovascular risk factors and duration of diabetes. Height and weight were measured and used to calculate body mass index. Waist circumference was measured at the level of the umbilicus and used as a measure of central obesity. Blood pressure was measured using a mercury sphygmomanometer and appropriate cuff size. After five minutes' rest in the sitting position, a set of three readings was taken five minutes apart. The average of the last two readings was taken as the patient's clinic blood pressure.[12] Hypertension was defined as blood pressure ≥ 140/90 mmHg or use of antihypertensive medication.

Fasting capillary blood glucose and glycated haemoglobin

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(HbA_{1c}) levels were measured on spot; blood glucose by a HemoCue AB glucose analyser (Angelholm, Sweden) and HbA_{1c} using a DCA 2000+ analyser (Bayer Inc., New York, USA). Urinary albumin/creatinine ratio (UACR) was measured in a spot morning urine sample using the same DCA 2000+ analyser, which measures urine albumin (in mg/l) and creatinine (in mg/dl) concentrations and calculates the urine albumin-to-creatinine ratio (UACR). Microalbuminuria was defined as UACR > 30 mg/g and macroalbuminuria as UACR > 300 mg/g.[13] Biochemical tests were performed with the use of a chemistry analyser (Abbott Architect, Illinois, USA) at Muhimbili National Hospital laboratory, which is the National reference laboratory.

All patients gave written informed consent. The study was ethically approved by the Muhimbili University of Health and Allied Sciences' research and publication committee.

All echocardiograms were performed by the same licensed cardiologist, who had received special training in echocardiography (PC), using a SONOS 7500 Phillips echocardiogram machine. Patients were examined in the left lateral decubitus position using a 3-MHz transducer. The echocardiographic protocol included parasternal long- and short-axis views of the left ventricle, left atrium and aorta, as well as two-, three- and four-chamber images of the left ventricle and pulsed Doppler recordings of LV filling. Spectral tissue Doppler was recorded of mitral annular plane velocity in the apical four-chamber view.

All images were recorded digitally on Magnetic Optical disks, and interpretation of all digital echocardiograms was done at the Department of Heart Diseases, Haukeland University Hospital using a Tomtec (TomTech Imaging Systems GmbH, Unterschielssheim, Germany) work station for post-processing. All studies were first read by the primary investigator and then proof read by the senior investigator, a highly experienced reader (EG).

Quantitative echocardiography was performed following the American Society of Echocardiography guidelines.[14] LV hypertrophy was considered present when LV mass indexed for $height^{2.7}$ exceeded 49.2 $g/m^{2.7}$ in men and 46.7 $g/m^{2.7}$ in women.[15] RWT was calculated as the ratio of end-diastolic posterior wall thickness to end-diastolic LV internal radius and considered increased if ≥ 0.43.

Patients were categorised into four LV geometric patterns based on LV $mass/height^{2.7}$ (LVMI) and RWT measurements in combination. Normal geometry was considered present if LVMI and RWT were both normal, concentric remodelling was the combination of normal LVMI and increased RWT, eccentric hypertrophy was the combination of LV hypertrophy and normal RWT, and concentric LV hypertrophy was present if LV hypertrophy and increased RWT were both present.[14]

LV circumferential end-systolic stress (CESS) was estimated at the midwall using a cylindrical model.[16] Myocardial contractility was assessed by midwall fractional shortening (MWS), calculated using a previously validated formula, taking into consideration the epicardial migration of the midwall during systole.[17] Stress-corrected fractional shortening (scFS) and stress-corrected MWS (scMWS) were calculated as the ratio between actual and predicted FS and MWS for actual CESS, respectively, using previously published equations.[17]

Transmitral flow was recorded with pulsed-wave Doppler between the mitral cusp tips in the apical four-chamber view. The early (E) and atrial (A) waves were traced for peak velocities and used to calculate the E/A ratio. Isovolumic relaxation time was measured from the leading edge of the aortic valve closure spike to the leading edge of the mitral valve high-intensity echo in five-chamber view. Early diastolic mitral annular plane velocity (E′) was measured by spectral tissue Doppler in the apical four-chamber view.[18]

Statistical analysis

Data management and statistical analysis was performed using SPSS for Windows version 18.0. Data are presented as mean ± SD for continuous variables and as percentages for categorical variables. Groups of patients were compared using the χ^2 test for categorical variables and unpaired Student's *t*-test, one way ANOVA with Sheffe's *post hoc* test or general linear model with Sidak's *post hoc* test for continuous variables, as appropriate. Bivariate correlations were assessed by Pearson's correlation coefficients. Covariates of increased RWT were identified in the total study population and in groups of type 1 and type 2 diabetes patients by multiple linear regression analyses, run with an enter procedure and co-linearity statistics. A two-tailed *p*-value ≤ 0.05 was considered statistically significant.

Results

The study population included 61 type 1 and 123 type 2 diabetes patients. Compared to type 1 patients, type 2 patients were older, had longer duration of diabetes and included more hypertensive and obese patients (all $p < 0.01$) (Table 1).

Compared to type 1 diabetes patients, type 2 patients had larger LV dimensions and higher RWT and LVMI (Table 2). LV systolic chamber function measured as stress-corrected fractional shortening and ejection fraction did not differ between the two groups, while myocardial contractility assessed by stress-corrected midwall shortening was significantly lower among type 2 diabetes patients (Table 2). Measures of diastolic function were also significantly unfavourable in the type 2 diabetes patients (Table 2). However, LV dimension and function did not differ between the two types of diabetes when adjustment for age and systolic blood pressure was done (Table 2).

In the total population, the prevalence of concentric remodelling, eccentric hypertrophy and concentric hypertrophy was 32, 8.3 and 23.7%, respectively. LV geometry differed significantly between type 1 and type 2 diabetes patients as a consequence of more type 2 diabetes patients having concentric LV hypertrophy (Fig. 1). Systolic blood pressure and body mass index were among the most important covariates of LV geometry in the total study population (Figs 2, 3).

In logistic regression analysis involving the total study population, LV hypertrophy (combined eccentric and concentric LV hypertrophy) was associated with obesity, (OR 3.97, 95% CI: 1.65–9.54, $p = 0.002$), hypertension (OR 4.58, 95% CI: 1.32–15.85, $p = 0.016$) and albuminuria (OR 2.31, 95% CI: 1.01–5.27, $p = 0.047$). This was independent of age, gender, type or duration of diabetes (Table 3).

The most prevalent types of abnormal LV geometry were concentric remodelling in type 1 diabetes patients and concentric LV hypertrophy in type 2 diabetes patients (Fig. 1). Overall, 58% of the total population had increased RWT. In univariate linear regression analysis, the most important correlates of higher RWT were older age, higher blood pressure and higher log

UACR, both in type 1 and type 2 diabetes patients (all $p < 0.05$) (Table 4). In addition, lower eGFR and high-density lipoprotein (HDL) cholesterol were significantly correlated with higher RWT among type 2 but not in type 1 diabetes patients. Having increased RWT was also associated with impaired systolic and diastolic LV function, including lower myocardial contractility, measured as scMWS, and delayed early LV diastolic relaxation, measured as longer IVRT, longer deceleration time and reduced E/A ratio, both in type 1 and type 2 diabetes patients (all $p < 0.05$) (Table 4).

When multivariate linear regression analyses were performed, higher systolic blood pressure, longer IVRT and low scMWS remained significant covariates of higher RWT both in type 1 and type 2 diabetes patients, irrespective of presence or absence of LV hypertrophy and also adjusted for CESS. In addition, low eGFR continued to be an independent covariate of higher RWT in type 2 diabetes patients. Substituting log UACR for eGFR in the type 1 diabetes patients' model did not give any independent association either (Table 5).

In binary logistic regression analysis, including type of diabetes, albuminuria, obesity, history of hypertension and HbA_{1c} level, the independent covariates of increased RWT were: type 2 diabetes (OR 2.7, 95% CI: 1.08–7.00), albuminuria (OR 2.2, 95% CI: 1.01–4.62), obesity (OR 2.6, 95% CI: 1.02–6.58) and hypertension (OR 2.5, 95% CI: 1.02–5.87), all $p < 0.05$.

A risk score was calculated based on the beta coefficients in this model: risk score = 9*x* (type of diabetes) + 8*x* (albuminuria) + 9*x* (obesity) + 9*x* (hypertension). For each parameter included in the score, a value of 1 was assigned if the variable was present

TABLE 1. DEMOGRAPHIC AND LABORATORY CHARACTERISTICS OF TYPE 1 AND TYPE 2 DIABETES PATIENTS

Characteristic	*Type 1* (n = *61*)	*Type 2* (n = *123*)	p-*value*
Age (years)	21.7 ± 10.6	55.0 ± 9.6	< 0.001
Females, *n* (%)	34 (55)	78 (64)	0.265
Duration of diabetes (years)	8.2 ± 4.5	10.7 ± 6.3	0.005
Body mass index (kg/m^2)	20.9 ± 4.4	28.4 ± 4.7	< 0.001
Obesity, *n* (%)	2 (3.3)	45 (36.6)	< 0.001
Waist circumference (cm)	74 ± 12	98 ± 11	< 0.001
Systolic blood pressure (mmHg)	117 ± 21	147 ± 22	< 0.001
Diastolic blood pressure (mmHg)	74 ± 14	88 ± 11	< 0.001
Hypertension, *n* (%)	11 (17.7)	100 (82.0)	< 0.001
Pulse pressure (mmHg)	43 ± 12	59 ± 17	< 0.001
Fasting blood glucose (mmol/l)	12.2 ± 4.4	10.4 ± 4.7	0.015
HbA_{1c} (%)	10.9 ± 2.2	9.8 ± 2.3	0.003
Total cholesterol (mmol/l)	4.7 ± 1.6	5.6 ± 1.5	0.001
HDL cholesterol (mmol/l)	1.2 ± 0.4	1.2 ± 0.3	0.855
LDL cholesterol (mmol/l)	3.2 ± 1.3	4.0 ± 1.4	< 0.001
Triglycerides (mmol/l)	1.6 ± 1.6	1.7 ± 1.0	0.617
Serum creatinine (µmol/l)	84 ± 70	106 ± 77	0.058
eGFR (ml/min/1.73 m^2)	106 ± 47	81 ± 24	< 0.001
Low eGFR, *n* (%)	6 (10)	21 (18)	0.268
Albuminuria, *n* (%)	24 (40.0)	39 (33.6)	0.412
Microalbuminuria, *n* (%)	16 (26.7)	33 (28.4)	0.860
Macroalbuminuria, *n* (%)	8 (13.3)	6 (5.2)	0.077

HbA_{1c} = glycated haemoglobin, HDL = high-density lipoprotein, LDL = low-density lipoprotein, eGFR = estimated glomerular filtration rate.

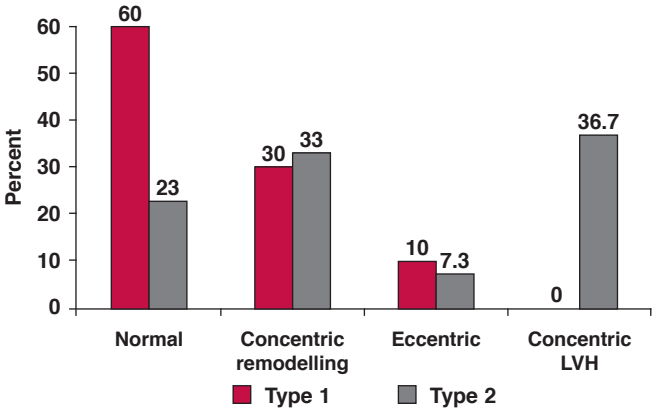

Fig. 1. LV geometric patterns in type 1 (red bars) and type 2 (grey bars) diabetes patients. The differences between normal geometry and concentric LVH were statistically significant, both $p < 0.001$.

TABLE 2. ECHOCARDIOGRAPHIC FINDINGS IN TYPE 1 AND TYPE 2 DIABETES PATIENTS

	Unadjusted			*Adjusted for age and systolic blood pressure*		
Echocardiographic finding	*Type 1* (n = *61*)	*Type 2* (n = *123*)	p-*value*	*Type 1* (n = *61*)	*Type 2* (n = *123*)	p-*value*
Interventricular septum in diastole (cm)	0.91 ± 0.21	1.27 ± 0.31	< 0.001	1.11 ± 0.06	1.16 ± 0.04	0.573
LV posterior wall in diastole (cm)	0.79 ± 0.17	1.06 ± 0.25	< 0.001	0.94 ± (.05	0.98 ± 0.03	0.622
LV end-diastolic diameter (cm)	4.01 ± 0.63	4.21 ± 0.58	0.036	4.10 ± 0.13	4.16 ± 0.08	0.769
Relative wall thickness	0.40 ± 0.10	0.52 ± 0.19	< 0.001	0.48 ± 0.04	0.48 ± 0.02	0.938
LV mass/height$^{2.7}$ (g/m$^{2.7}$)	33.0 ± 9.6	49.2 ± 16.8	< 0.001	40.6 ± 3.0	45.1 ± 1.8	0.299
Fractional shortening (%)	37 ± 5	35 ± 6	0.176	36 ± 1.3	36 ± 0.8	0.940
Stress-corrected fractional shortening (%)	99 ± 11	99 ± 16	0.942	100 ± 3	99 ± 2	0.739
Ejection fraction (%)	65 ± 7	63 ± 8	0.328	63 ± 2	64 ± 1	0.554
Midwall shortening (%)	16 ± 3	13 ± 3	< 0.001	14 ± 0.7	15 ± 0.4	0.875
Stress-corrected midwall shortening (%)	90 ± 17	74 ± 18	< 0.001	80 ± 3.8	81 ± 2.4	0.918
Transmitral E/A ratio	1.5 ± 0.4	0.9 ± 0.3	< 0.001	1.2 ± 0.8	1.1 ± 0.5	0.226
Deceleration time (ms)	165 ± 52	206 ± 61	< 0.001	191 ± 13	192 ± 8	0.954
Isovolumic relaxation time (ms)	62 ± 16	81 ± 20	< 0.001	78 ± 3.8	73 ± 2.4	0.378
Early tissue Doppler velocity (E′) (cm/s)	10.3 ± 2.3	6.5 ± 2.4	< 0.001	8.3 ± 0.5	7.5 ± 0.3	0.305
E/E′ ratio	9.5 ± 2.4	11.7 ± 4.4	< 0.001	11.2 ± 0.8	10.8 ± 0.5	0.733

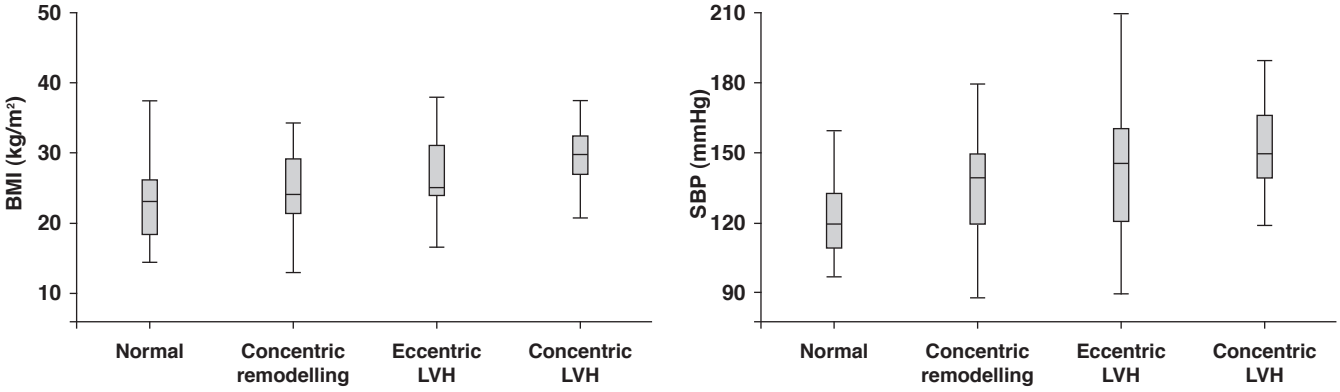

Fig. 2. LV geometry in relation to body mass index and systolic blood pressure, and impact on comparison between the different LV geometric patterns; $p < 0.001$ for comparison of body mass index (left panel) and systolic blood pressure (right panel) in the four geometric patterns by ANOVA.

TABLE 3. INDEPENDENT PREDICTORS OF LV HYPERTROPHY IN THE TOTAL POPULATION BY LOGISTIC REGRESSION ANALYSIS

Variable	*Odds ratio (95% CI)*	*p-value*
Obesity	3.97 (1.65–9.54)	0.002
Hypertension	4.58 (1.32–15.85)	0.016
Albuminuria	2.31 (1.01–5.27)	0.047
Age (years)	1.03 (0.98–1.08)	0.206
Male gender	0.66 (0.28–1.53)	0.329
Type of diabetes (type 1 vs type 2)	0.73 (0.13–4.17)	0.727
Duration of diabetes (years)	0.99 (0.92–1.06)	0.785

or 0 if it was absent. Therefore the individual risk score varied in this study population between 0 and 35 points. Based on the ROC curve analysis, the optimal cut-off point for the prediction of increased RWT was a score of 13 points (area under the curve = 0.77, $p < 0.001$, sensitivity = 76% and specificity = 67%). This risk score had a positive predictive value of 76% (Fig. 4).

Discussion

From echocardiographic studies in Caucasians, North American Indians and African Americans, it is well known that diabetes is associated with concentric LV remodelling, and LV hypertrophy is particularly common in patients with combined type 2 diabetes and hypertension.[19,20] However, few studies have reported on LV geometry in diabetic populations from sub-Saharan Africa. Therefore, the present study is among the few to report on prevalence and covariates of abnormal LV geometry in diabetic sub-Saharan African patients.

The study has many interesting findings, adding to current knowledge on diabetic heart disease in Africans, in particular (1) that abnormal LV geometry is common in sub-Saharan African

TABLE 4. CORRELATES OF RWT IN THE TOTAL POPULATION AND IN TYPE 1 AND TYPE 2 DIABETES PATIENTS

	Total population		*Type 1*		*Type 2*	
	r	p-*value*	*r*	p-*value*	*r*	p-*value*
Age (years)	0.391	< 0.001	0.357	0.005	0.203	0.035
Body mass index (kg/m²)	0.237	0.002	0.068	0.605	0.031	0.752
Systolic blood pressure (mmHg)	0.383	< 0.001	0.359	0.004	0.234	0.015
Diastolic blood pressure (mmHg)	0.388	< 0.001	0.331	0.009	0.282	0.003
Fasting blood glucose (mmol/l)	0.029	0.705	0.204	0.118	0.068	0.485
HbA_{1c} (%)	–0.009	0.909	0.113	0.390	0.066	0.496
eGFR (ml/min/1.73 m²)	–0.282	< 0.001	–0.076	0.563	–0.319	0.001
HDL cholesterol (mmol/l)	–0.165	0.033	–0.146	0.265	–0.277	0.002
Triglycerides (mmol/l)	0.134	0.082	0.279	0.031	0.079	0.416
Triglyceride-to-HDL cholesterol ratio	0.108	0.163	0.141	0.287	0.175	0.069
Log UACR (mg/g)	0.147	0.059	0.259	0.048	0.194	0.045
E′ (cm/sec)	–0.434	< 0.001	–0.149	0.246	–0.377	< 0.001
LV mass/height$^{2.7}$ (g/m$^{2.7}$)	0.477	< 0.001	0.113	0.389	0.426	< 0.001
E/A ratio	–0.382	< 0.001	–0.321	0.012	–0.241	0.012
Deceleration time (ms)	0.313	< 0.001	0.255	0.047	0.228	0.017
Isovolumic relaxation time (ms)	0.428	< 0.001	0.304	0.017	0.347	< 0.001
Circumferential end-systolic stress (dyne/cm²)	–0.421	< 0.001	–0.349	0.006	–0.557	< 0.001
Midwall shortening (%)	–0.717	< 0.001	–0.619	< 0.001	–0.723	< 0.001
Stress-corrected midwall shortening (%)	–0.755	< 0.001	–0.675	< 0.001	–0.759	< 0.001
E/E′	0.299	< 0.001	–0.158	0.228	0.293	0.002

HbA_{1c} = glycated haemoglobin, eGFR = estimated glomerular filtration rate, HDL = high-density lipoprotein, UACR = urine albumin creatinine ratio.

TABLE 5. INDEPENDENT COVARIATES OF HIGHER RWT IN TOTAL POPULATION AND IN TYPE 1 AND TYPE 2 DIABETES PATIENTS

	Total population ($R^2 = 0.69$*)		*Type 1* ($R^2 = 0.73$*)		*Type 2* ($R^2 = 0.66$*)	
Covariate	*ß*	p-*value*	*ß*	p-*value*	*ß*	*p value*
Systolic blood pressure (mmHg)	0.301	< 0.001	0.442	< 0.001	0.233	0.001
Low eGFR (ml/min/1.73 m^2)	0.131	0.007	0.009	0.909	0.150	0.024
Low stress-corrected MWS (%)	0.239	< 0.001	0.493	< 0.001	0.156	0.017
Isovolumic relaxation time (ms)	0.170	0.001	0.180	0.041	0.155	0.016
LV mass/height$^{2.7}$	0.187	0.001	0.091	0.284	0.189	0.008
Circumferential end-systolic stress (dyne/cm^2)	–0.584	< 0.001	–0.682	< 0.001	–0.602	< 0.001
Male gender	0.083	0.065	–0.009	0.905	0.123	0.051

eGFR = estimated glomerular filtration rate, MWS = midwall shortening, *$p < 0.001$.

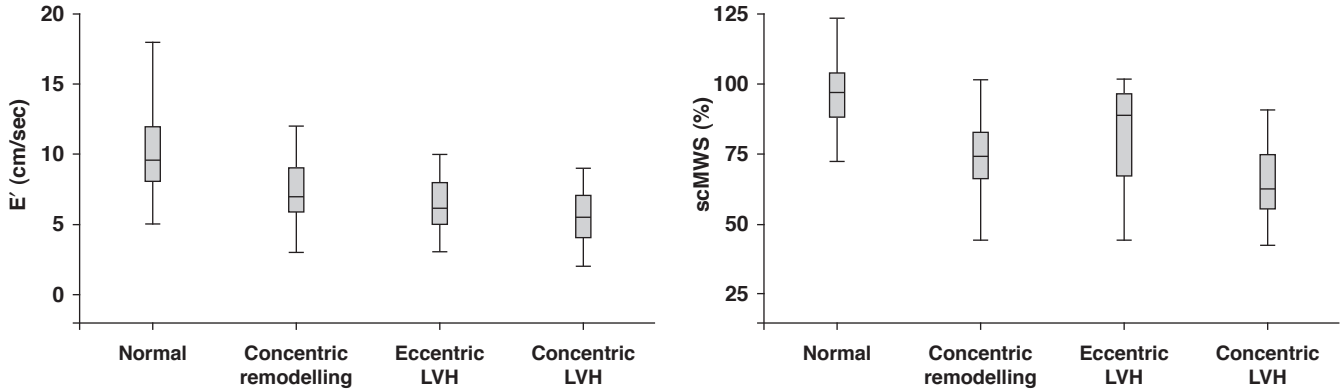

Fig. 3. Early tissue Doppler velocity (E′) and stress-corrected midwall shortening (scMWS) in relation to LV geometric patterns; $p < 0.001$ for comparison of E′ (left panel) and scMWS (right panel) in the four geometric patterns by ANOVA.

diabetic patients, (2) that concentric remodelling was the most prevalent abnormal LV geometric pattern in this population and associated with reduced LV myocardial contractility and delayed diastolic relaxation, and (3) that a simple algorithm combining everyday clinical and laboratory assessment may be used to identify diabetic patients with high risk of cardiac target-organ damage.

Our findings add to a previous report by Ojji *et al.* on Nigerians with type 2 diabetes.[21] In their study of 122 patients, abnormal LV geometry was found in 51% of patients, compared to 74% in the present study. Of note, the study by Ojji *et al.*[21] only included normotensive type 2 diabetes patients, and as demonstrated by our findings, hypertension was a strong covariate of having both LV hypertrophy and increased RWT, probably explaining the higher prevalence of abnormal LV geometry in the present study. As demonstrated, age and systolic blood pressure were the main confounders explaining the difference in LV structure between groups of patients with type 1 or type 2 diabetes.

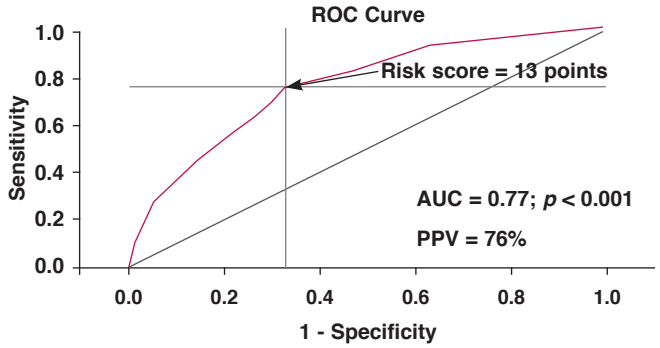

Fig. 4. Receiver-operator characteristic (ROC) curve for the clinical risk score with best sensitivity (76%) and specificity (67%) in predicting high relative wall thickness. The cut-off value for the risk score (13 points) identified by the ROC analysis is indicated by an arrow. AUC = area under the curve, PPV = positive predictive value.

Hypertension, in particular isolated systolic hypertension, increases in prevalence with aging, mainly as a consequence of arterial stiffening imposing increased load on the left ventricle. Older age has been documented to be particularly associated with increased RWT, and with LV hypertrophy when hypertension coexists.[22-24] However, despite differences in socio-demographic backgrounds, our results were comparable to those reported by Eguchi *et al.* from Japanese hypertensive patients with type 2 diabetes. In their study, including 161 patients, the prevalence of concentric remodelling, eccentric hypertrophy and concentric hypertrophy, respectively, were 29, 16 and 39%.[25]

We found no previous echocardiographic study on LV geometric patterns performed among type 1 diabetes patients from sub-Saharan Africa, and our study is probably the first to describe LV geometry in such patients. As demonstrated by our results, abnormal LV geometry was found in 40% of type 1 diabetes patients. Specifically, 30% of type 1 diabetes patients had concentric remodelling, and this was the most common type of abnormal LV geometry in this group. All six type 1 diabetes patients (10%) with LV hypertrophy had eccentric LV hypertrophy.

Interestingly, none of the type 1 diabetes patients had concentric LV hypertrophy, the most common abnormal LV geometric pattern found among type 2 diabetes patients in the present study. This finding could probably be explained by the low prevalence of hypertension among type 1 diabetes patients in our study (18 vs 82%). Other investigators have reported a higher

prevalence of LV hypertrophy among type 1 diabetes patients with nephropathy.[26]

Of note, in the present study population, all type 1 diabetes patients with LV hypertrophy also had albuminuria (results not shown), and albuminuria was identified as a main covariate of LV hypertrophy in multivariate analysis. The beneficial impact of renin–angiotensin inhibition on albuminuria and the prevention of overt renal failure has previously been demonstrated in type 1 diabetes patients with microalbuminuria.[27] Whether the prevention of progression to overt renal failure with the use of drugs that inhibit the renin–angiotensin system will also prevent progression to LV hypertrophy among type 1 diabetes patients is a question that needs to be answered in future prospective studies in Africans.

The finding that higher RWT was significantly associated with older age and higher blood pressure agree with previous reports from epidemiological studies in North American Indians.[3] Importantly though, as demonstrated by multivariate analysis in our study, independent associations between increased RWT and measures of systolic and diastolic LV function were found irrespective of presence or absence of LV hypertrophy or hypertension. This is an important finding because it emphasises the need to further stratify patients into the different LV geometric patterns, rather than by presence or absence of LV hypertrophy alone. The finding is particularly important in the African diabetes context, as concentric remodelling (increased RWT with normal LVMI) was found to be the most common abnormal LV geometric pattern in the present study, as also previously reported among African American hypertensive patients.[4]

In 884 children and adolescents with a high prevalence of obesity, Di Bonito *et al*. found that higher triglyceride-to-HDL cholesterol ratio independently predicted higher RWT and concentric LV hypertrophy.[28] In our study, lower serum HDL cholesterol levels, but not triglyceride-to-HDL cholesterol ratio, were associated with higher RWT in type 2 diabetes patients, only in univariate analysis. The differential findings probably reflect differences in prevalence of obesity and degree of myocardial fat storage between the two populations.[29]

In the LIFE study, concentric remodelling was associated with a three and eight times increased risk of stroke and cardiovascular death after 4.8 years of follow up, respectively.[30] So, in a way, our findings may be explaining the link between the increased prevalence of congestive heart failure and stroke seen among black diabetic patients.[31]

Of note, an independent association between gender and measures of LV geometry was not found in the present study population, partly contrasting with findings in African Americans participating in the Atherosclerosis Risk in Community (ARIC) study, which reported that diabetic women had more concentric LV geometry, but similar prevalence of LV hypertrophy as men.[32]

We have shown that a simple algorithm using every-day clinical and laboratory tests (type of diabetes, hypertension, obesity and albuminuria) may be used to identify three out of four high-risk diabetic patients with increased RWT. This is very important in a setting such as Tanzania where echocardiography is not readily available. Of note, following this algorithm, a patient with type 2 diabetes with any of the other three risk factors, or a type 1 diabetes patient having any two of the other three risk factors will have a 76% chance of having cardiac target-organ damage as well.

Conclusion

We have shown that abnormal LV geometry was common in this diabetic population. In particular, increased RWT was present in 58% of patients and demonstrated as a marker of subclinical cardiac target-organ damage. Furthermore, using the clinical risk factors, type of diabetes, hypertension, obesity and albuminuria, 76% of diabetic patients with increased RWT can be identified.

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Association of waist circumference, body mass index and conicity index with cardiovascular risk factors in postmenopausal women

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Abstract

In menopause, changes in body fat distribution lead to increasing risk of cardiovascular disease and metabolic disorders. The aim of this study was to assess the association of adiposity using the conicity index (CI), body mass index (BMI) and waist circumference (WC) with cardiovascular risk factors (hypertension, diabetes and dyslipidaemia). The sample of this cross-sectional study was collected from June to October 2010 and 165 consecutive menopausal women who had attended the Health and Treatment Centre and Endocrine Research Centre of Firoozgar Hospital in Tehran, Iran were assessed. Age, weight, height, WC, waist–hip ratio (WHR), CI and fat mass were measured. Systolic and diastolic blood pressure (SBP and DBP), fasting blood glucose, insulin, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and total cholesterol (TC) levels were also determined. All statistical analyses were performed by SPSS version 17 (SPSS Inc, Chicago, IL, USA).

Results showed that BMI was positively and significantly associated with SBP ($r = 0.21$; $p = 0.009$). WC was positively and significantly correlated with SBP ($r = 0.26$; $p = 0.02$) and DBP ($r = 0.16$; $p = 0.05$). WHR was also significantly and positively associated with SBP ($r = 0.29$; $p = 0.001$). Age and WC were associated with CI quartiles at the 0.05 significance level. The correlation of CI quartiles with SBP and weight were at the 0.01 significance level.

We showed a significant association of WC with SBP and DBP, and that BMI could be an important determining factor of SBP. For assessing the association between CI and cardiovascular risk factors, future studies with larger sample sizes are recommended.

Keywords: body mass index, cardiovascular risk factors, conicity index, waist circumference

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Epidemiological studies have found a progressive increase in the prevalence of cardiovascular risk factors (dyslipidaemia, elevated blood pressure, disturbances in glycaemic control) with increasing body fatness.[1-3] In recent decades, many prospective and cross-sectional studies using anthropometric measures have been undertaken in order to understand the relationship between obesity and cardiovascular risk factors. Various obesity measurements such as body mass index (BMI), waist circumference (WC) and waist-to-hip ratio (WHR) were investigated. However, the best obesity measure to use as a predictor of cardiovascular risk factors remains elusive.[4-5]

BMI is the most commonly used and simple measure of body size, especially for estimating the frequency of obesity in large epidemiological studies.[6] This index cannot however be used for the evaluation of body fat distribution and abdominal fat mass. It has been shown that intra-abdominal fat has a stronger relationship with risk of obesity-related morbidity than with overall adiposity.[7] Therefore WHR and WC measurements can be used as valid alternatives to BMI for the evaluation of intra-abdominal mass and total fat.[8]

A study by Huang and co-workers showed that WHR and WC measurements were strongly associated with incidence of coronary heart disease, independent of BMI.[9] However the validity of WHR measurements has been questioned as an indicator of abdominal adipose tissue distribution.[10]

Another index of abdominal adiposity is the conicity index (CI). This has a theoretical range, includes a built-in adjustment of waist circumferences for height and weight, and does not require the hip circumference to assess fat distribution.[11,12]

In menopause, changes in body fat distribution lead to increasing risk of cardiovascular and metabolic diseases. Increase in abdominal obesity together with acceleration of the breakdown of lean body mass means there is no significant change in the body weight of postmenopausal women.[7,8]

Since the prediction of cardiovascular disease by the presence of risk factors is of such importance, anthropometric indices are seen as useful indicators to achieve this. The aim of this study was to assess the association of adiposity using the conicity index, BMI and WC, with cardiovascular risk factors (hypertension, diabetes and dyslipidaemia).

Methods

This cross-sectional study was carried out from June to October 2010. Using the non-probability convenience method, 165 consecutive menopausal women who had attended the Health and Treatment Centre and Endocrine Research Centre of Firoozgar Hospital in Tehran, Iran, were invited to participate. Subjects were informed on the objectives of the study. The study was approved by the ethics committee of the Medical School of Iran University of Medical Sciences.

Inclusion criteria for the study were: being naturally menopausal for at least one year, non-smokers, and having a BMI

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less than 30 kg/m^2. We excluded women with severe liver, renal and cardiovascular disorders, and those who were on medication. Women on hormone replacement or lipid-reducing therapy, antihypertensive drugs and non-steroidal anti-inflammatory drugs (NSAIDs) were also excluded.

Variables included age, weight, height, WC, WHR, CI and fat mass. Systolic and diastolic blood pressure, and laboratory variables including fasting blood glucose, insulin, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and total cholesterol (TC) levels were measured. All participants were asked to complete a three-day dietary-recall questionnaire and a food-frequency questionnaire.

Weight, height, and hip and waist circumference were measured using standard procedures. Weight was measured to the nearest to 0.1 kg, without shoes and wearing light clothing. Height was recorded to the nearest 0.1 cm. WC was measured using a rubber measuring tape, horizontally halfway between the lower border of the rib cage and the iliac crest. Hip circumference (HC) was measured at the widest part over the buttocks. WC and HC were measured to the nearest 0.5 cm. The WHR was calculated by dividing the WC (cm) by the HC (cm). BMI was determined as weight (kg) divided by height (m^2). The CI was calculated using weight (kg), height (m) and WC (m) as follows:

$$\text{Conicity index} = \frac{\text{waist circumference (m)}}{\sqrt{0.109}\sqrt{\text{weight (kg)/height (m)}}}$$

Fat mass was determined by BIA (Body Stat, UK). Blood pressure was measured after 10 minutes' rest, with the subjects in a seated position. Systolic and diastolic blood pressure (SBP and DBP, respectively) were measured with two readings at one-minute intervals. The mean was the average of two readings. All measurements were recorded to the nearest 2 mmHg.

Following at least 12 hours' fast, blood was taken for assessment of total cholesterol (TC), fasting blood glucose (FBS), triglyceride, HDL-C and LDL-C levels. These were determined by enzymatic procedures (Pars Azmon Kit, Tehran, Iran). Plasma insulin level was measured by ELISA (Diaplus Inc. Kit, North York, ON, Canada).

Diabetes was defined as a history of diabetes diagnosed by a physician, taking hypoglycaemic medication, or having a FBS level more than 126 mg/dl.

Statistical analyses

Descriptive statistics for variables were used with tables, means and standard deviations. The association of WC, WHR and CI with lipid profiles, blood pressure, serum insulin and FBS levels was determined with Pearson's correlation coefficient. One-way analysis of variance (ANOVA) was used for assessing associations between cardiovascular risk factors (diabetes, blood pressure and dyslipidaemia) and CI quartiles. Because there were few cases of diabetes, FBS level was used as a proxy of diabetes association with CI. All statistical analyses were performed by SPSS version 17 (SPSS Inc, Chicago, IL, USA). A p-value < 0.05 was considered significant.

Results

Data of 150 menopausal women were completed and included in the final analysis in this study (response rate 91%). The mean age of the women was 56.8 years (± 7.64) with a range of 42 to 80 years. With regard to education, 85.2% of subjects were literate. The majority of participating women were housewives (86.7%) and 79.3% were married. Only eight women (5.4%) had diabetes, based on our definition. The physical and laboratory characteristics of the women are shown in Table 1. Table 2 illustrates the correlation matrix of the variables.

Results show that BMI was positively and significantly associated with SBP (r = 0.21; p = 0.009). WC was positively and significantly correlated with SBP (r = 0.26; p = 0.02) and DBP (r = 0.16; p = 0.05). WHR was positively and significantly associated with SBP (r = 0.29; p = 0.001). CI had a positive correlation with SBP (r = 0.22; p = 0.009). The association of CI with FBS (r = –0.16) and triglycerides (r = –0.17) was weak and negatively significant.

Because of the small number of subjects with diabetes in this study, the association between anthropometric measures and this risk factor for cardiovascular disease was not assessed. Table 3 shows the risk factor for cardiovascular disease and anthropometric measures according to quartiles of CI. This table shows that age and WC were associated with CI quartiles at the 0.05 significance level. The correlation of CI quartiles with SBP and weight were at the 0.01 significance level.

Discussion

In this cross-sectional study, 165 postmenopausal women were randomly selected from the Health and Treatment Centre and Endocrine and Metabolism Research Centre of Firoozgar Hospital of Tehran University of Medical Sciences. Correlations of BMI, WC and CI with cardiovascular risk factors (hypertension, serum LDL-C and HDL-C, glucose and insulin levels) were assessed. WC had a significant correlation with SBP and DBP. BMI had a significant correlation with SBP only. CI had a significant correlation with SBP.

The findings of our study was similar to those of Taratchuk and co-workers.[13] They reported that WC and CI were superior to BMI for identifying visceral adiposity, metabolic disorders and cardiovascular risk factors.[13]

TABLE 1. PHYSICAL AND LABORATORY CHARACTERISTICS OF THE STUDY POPULATION

Variables	*Mean*	*SD*	*Min*	*Max*
Weight (kg)	64.58	8.10	45.00	84.00
Height (cm)	156.88	6.19	142.00	178.00
BMI (kg/m^2)	26.11	2.93	18.50	36.00
Waist circumference (cm)	87.18	9.07	67.00	107.00
Hip circumference (cm)	103.11	6.80	88.00	122.00
Waist–hip ratio	0.84	0.07	0.68	1.09
Systolic blood pressure (mmHg)	11.59	1.46	9.00	19.00
Diastolic blood pressure (mmHg)	7.49	0.96	6.00	11.00
Fasting blood sugar (mg/dl)	97.14	43.26	70.00	380.00
Plasma insulin level	8.19	4.26	1.10	24.40
Total cholesterol (mg/dl)	193.14	45.38	110.00	350.00
Triglycerides (mg/dl)	215.02	105.22	70.00	620.00
LDL-C (mg/dl)	111.81	41.93	21.30	260.00
HDL-C (mg/dl)	38.84	6.93	26.00	60.00
Fat mass	43.15	78.69	20.70	69.99
Conicity index	1.24	0.09	1.04	1.50

BMI: body mass index, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol; SD: standard deviation.

TABLE 2. CORRELATION MATRIX WITH PEARSON CORRELATION COEFFICIENT OF MEASURED VARIABLES

	BMI	*WC*	*WHR*	*SBP*	*DBP*	*FBS*	*PIL*	*TC*	*TG*	*HDL-C*	*LDL-C*	*FM*	*CI*
BMI	–	0.67*	0.33*	0.21*	0.10	–0.06	–0.10	–0.11	–0.06	0.01	–0.04		0.31*
WC	–	–	–	0.26*	0.16*	–0.15	–0.08	–0.06	–0.12	–0.07	–0.04		0.86*
WHR	–	–	–	0.29*	0.10	–0.15	–0.03	–0.00	–0.15	–0.03	0.03	–0.00	0.84*
SBP	–	–		–	–	–0.05	–0.22*	0.20*	0.00	0.13	0.16*		0.22*
DBP	–	–		–	–	0.01	–0.15	0.10	0.04	0.11	0.04		0.08
FBS	–	–		–		–	0.23*	0.41*	0.28*	0.30*	0.29*		–0.16*
PIL						–	–	–0.06	0.29*	–0.09	–0.13		–0.07
TC	–	–	–	–	–	–	–	–	0.28*	0.15	0.84*		–0.06
TG	–	–	–	–	–	–	–	–	–	0.03	–0.06		–0.17*
LDL-C	–	–	–	–	–	–	–	–	–	–	–		–0.00
HDL-C	–	–	–	–	–	–	–	–	–	–	–		–0.07
FM													

BMI: body mass index, WC: waist circumference, WHR: waist–hip ratio, SBP: systolic blood pressure, DBP: diastolic blood pressure, FBS: fasting blood sugar, PIL: plasma insulin level, TC: total cholesterol, TG: triglycerides, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, FM: fat mass. *$p < 0.05$.

Alemedia recommended a cut-off point of 86 cm for WC, 0.87 for WHR and 1.25 for CI as indicators of increased occurrence of cardiovascular risk factors, despite the lack of consensus between studies.[14] Other studies gave 1.18 as the best cut-off point for CI. Almeida reported that CI had the highest sensitivity and specificity for predicting the occurrence of cardiovascular risk factors.[14] In our study, the postmenopausal women had a mean WC of 87.1 ± 9 cm, WHR of 0.85 ± 0.07 and CI of 1.24 ± 0.9, which verified the use of central obesity to indicate a high probability of the occurrence of cardiovascular risk factors in these participants.

Zhou *et al*. reported that BMI, WC and CI had an association with blood pressure but WC in men and BMI in women had the highest association with blood pressure.[15] In our study, only BMI had a significant association with SBP. In comparison to our study, Zhou's study was done on a larger population (29 179 vs 150 participants). Zhou indicated that visceral obesity, measured by WC or WHR was more closely associated with blood pressure and/or the presence of hypertension than overall obesity, measured by BMI. Furthermore, the linear regression coefficient for each obesity measurement with continuous SBP or DBP was substantially greater in men than in women, suggesting a greater male responsiveness of blood pressure to a gain than weight or abdominal deposition.[15]

Dalton reported a higher association of BMI with blood pressure and LDL-C and HDL-C levels compared to WC. However, he had more participants compared to our study (11 247 vs 150 persons) and he did not make use of conicity index.[8] Neufeld reported the best cut-off points for pre-diabetes status as 27.8 kg/m^2 for BMI, 89.8 cm for WC and 1.28 for CI. In his study, BMI had more sensitivity and specificity with pre-hydration and pre-diabetes compared to WC and CI, but his study was carried out on under 35-year-old pre-menopausal women.[16]

The results of the studies by Ghosh, and Sanchez Viveros *et al.* in postmenopausal and elderly subjects, respectively, was consistent with our study. They reported that CI had a higher association with type 2 diabetes compared to BMI and WC.[17,18] On the other hand, Ghosh indicated a significant difference between central obesity and fat-free mass among normotensive and hypertensive subjects, although their level of obesity was similar.[17] Hypertensive individuals had significantly enhanced levels of central body fat distribution, which was consistent with the findings of our study.

TABLE 3. MEASURED VARIABLES (MEAN AND SD) OF STUDY SUBJECTS ACCORDING TO QUARTILES OF CI

	CI			
Variables	*1st Q < 1.18* (n = *37*)	*2nd Q 1.18 > 1.23* (n = *38*)	*3rs Q 1.23 < 1.31* (n = *38*)	*4th Q ≥ 1.31* (n = *37*)
Age*	55.37 (7.33)	55.76 (6.56)	56.29 (5.40)	60.18 (9.87)
Weight (kg)**	61.67 (7.56)	64.92 (8.82)	65.78 (7.03)	66.10 (8.24)
Height (cm)	157.62 (5.27)	157.26 (5.55)	156.72 (6.23)	156.02 (7.65)
SBP (mmHg)**	11.13 (1.31)	11.69 (1.70)	11.51 (1.36)	12.01 (1.37)
DBP (mmHg)	7.35 (1.06)	7.68 (0.98)	7.24 (0.98)	7.67 (0.74)
Waist (cm)*	77.29 (6.24)	84.39 (5.13)	89.75 (4.86)	97.43 (5.25)
FBS (mg/dl)	109.81 (69.33)	90.71 (24.57)	101.78 (42.76)	86.89 (11.99)
TC (mg/dl)	200.02 (49.44)	192.00 (45.57)	185.64 (43.53)	192.70 (41.93)
TG (mg/dl)	251.78 (135.79)	202.81 (87.87)	197.48 (98.54)	201.78 (80.97)
HDL-C (mg/dl)	40.45 (7.29)	38.63 (7.95)	37.27 (6.14)	39.00 (6.13)
LDL-C (mg/dl)	113.40 (43.12)	112.42 (45.90)	105.62 (37.53)	114.20 (41.25)

SBP: systolic blood pressure, DBP: diastolic blood pressure, FBS: fasting blood sugar, TC: total cholesterol, TG: triglycerides, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol. *$p < 0.05$, **$p < 0.01$.

A few studies reported that waist-to-height ratio and sagital abdominal diameter had the highest association with serum lipoprotein cholesterol levels and blood pressure.[19,20] However we did not measure these two parameter but suggest that future studies do so.

Our study had some limitations. The most important was the small sample size, resulting in too few diabetic patients. This was due to difficulties in getting women to participate in the study. However, a sample size of 100 should be enough to assess the correlation between variables within one group.

Another limitation was the nature of cross-sectional studies, which are not able to determine temporality. Therefore we could not identify whether the risk factors of cardiovascular disease preceded increased adiposity, or increased adiposity was the result of these risk factors (dyslipidaemia, diabetes and hypertension). We suggest future studies with prospective designs are necessary to identify this enigma.

Conclusion

We showed a significant association of WC with SBP and DBP, which are important risk factors for cardiovascular disease. We also indicated BMI could be an important determining factor of SBP. Although we showed a significant association between CI and SBP, it did not have enough power and more investigations are necessary.

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Accuracy of D-dimer:fibrinogen ratio to diagnose pulmonary thromboembolism in patients admitted to intensive care units

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Abstract

Introduction: **Pulmonary thromboembolism (PTE) may increase D-dimer and decrease fibrinogen levels. However, in settings such as intensive care units (ICU) and in long-term hospitalised patients, several factors may influence D-dimer and fibrinogen concentrations and make them unreliable indicators for the diagnosis of PTE. The aim of this study was to evaluate the accuracy of D-dimer:fibrinogen ratio (DDFR) for the diagnosis of PTE in ICU patients.**

Methods: **ICU patients who were suspected of having a first PTE and had no history of using anti-coagulants and contraceptives were included in the study. Levels of D-dimer and fibrinogen were measured for each patient prior to any intervention. Angiography or CT angiography was done in order to establish a definite diagnosis for each patient. Suitable analytical tests were performed to compare means.**

Results: **Eighty-one patients were included in the study, of whom 41 had PTE and 40 did not. Mean values of D-dimer and fibrinogen were 3.97 ± 3.22 μg/ml and 560.6 ± 197.3 mg/dl, respectively. Significantly higher levels of D-dimer (4.65 ± 3.46 vs 2.25 ± 2.55 μg/ml, $p = 0.006$) and DDFR (0.913 ± 0.716 vs 483 ± 0.440 × 10^{-3}, $p = 0.003$) were seen in PTE patients than in those without PTE. Receiver operating characteristic (ROC) analysis showed a 70.3% sensitivity and 70.1% specificity with a D-dimer value of 2.43 μg/ml (AUC = 0.714, $p = 0.002$) as the best cut-off point; and a 70.3% sensitivity and 61.6% specificity with a DDFR value of 0.417 × 10^{-3} (AUC = 0.710, $p = 0.004$) as the best cut-off point. In backward stepwise regression analysis, DDRF (OR = 0.72, $p = 0.025$), gender (OR = 0.76, $p = 0.049$) and white blood cell count (OR = 1.11, $p = 0.373$) were modelled ($p = 0.029$, $R^2 = 0.577$).**

Conclusion: **For diagnosis of PTE, DDFR can be considered to have almost the same importance as D-dimer level. Moreover, it was possible to rule out PTE with only a D-dimer cut-off value < 0.43 mg/dl, without the use of DDFR. However, these values cannot be used as a replacement for angiography or CT angiography**

Keywords: D-dimer, fibrinogen, pulmonary thromboembolism, intensive care unit (ICU)

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Pulmonary thromboembolism (PTE) is the third most common cause of cardiovascular-related deaths, with an average incidence of one in 100 000 patients annually.[1,2] PTE is also one of the most important causes of sudden death and occurs in 10% of hospitalised patients, of which only 29% are correctly diagnosed before death.[3] Moreover, PTE is a common life-threatening complication in patients with long-term hospitalisation, especially in intensive care units (ICU).[4]

The signs and symptoms of PTE are often very non-specific and can lead the practitioner to misdiagnose it.[5] Although computed tomographic (CT) angiography is a first-line method for the diagnosis of PTE, it is contra-indicated in patients with renal insufficiency and in pregnant women, and it is relatively expensive, especially for developing countries. These limitations can result in mismanagement of PTE.[5] Therefore attempts have been made for years to find a less-invasive, well-priced and more available test, such as biochemical markers in plasma.[7-10]

D-dimer is a degradation product of cross-linked fibrin that increases in acute thromboembolic events.[11] D-dimer concentrations can be used to diagnose or rule out PTE but its specificity is poor because D-dimer levels can be elevated in other clinical conditions associated with additional fibrin formation, including old age, malignancies, infections and postoperative states.[12,13]

Plasma fibrinogen is one of the most important factors in the coagulation cascade and its concentration rises in many conditions, such as haemodynamic impairment, infections, cardiac, lung and aortic diseases and malignancies, as an acute-phase reactant. Many of these conditions have signs and symptoms similar to those of PTE.[14,15]

A study by Kucher *et al*. demonstrated that the D-dimer:fibrinogen ratio could be a specific predictor for PTE in emergency patients with no other medical condition.[9] However, in other settings such as the ICU or in long-term hospitalised patients with an elevated risk for PTE, several

factors may influence D-dimer and fibrinogen concentrations.[12-16] Furthermore, in these patients, there was less accessibility to CT angiography and more complications were experienced with the use of it.[17,18] The aim of this study was to evaluate the reliability of the D-dimer:fibrinogen ratio (DDFR) for the diagnosis of PTE in ICU patients.

Methods

In this analytical cross-sectional study, 91 critically ill patients admitted to the ICU wards of Rasoul-e-Akram and Shahid-Rajaee hospitals were included. All of the patients were diagnosed with diseases such as heart failure, pneumonia and stroke at the time of hospitalisation. To enrol these patients in our study, they had to be susceptible to a first PTE in the ICU setting, and showing signs and symptoms of PTE.

Diagnosis was established by angiography or CT angiography. The patients with documented PTE were included in our case group and those without PTE were used as the control group. Patients with a history of using anticoagulants or oral contraceptives, and those with a previous history of PTE were excluded.

Prior to any treatment or invasive diagnostic studies, blood samples were taken from all patients for routine laboratory tests such as a complete blood cell count (CBC), arterial blood gas (ABG), and plasma sodium (Na), potassium (K), D-dimer and fibrinogen levels. Medical history and other demographic information were collected from patients' medical files and inserted into pre-prepared checklists.

For D-dimer and fibrinogen assays, 2.7 ml of blood was taken from the antecubital vein of all patients, placed in standard Vacutainer (Becton Dickinson, Plymouth, UK) tubes containing 0.109 M buffered tri-sodium citrate, and centrifuged at 1 000 × *g* for 10 minutes at 18–21°C to extract the plasma. The samples were then sent to the laboratory in a cold box.

All biochemical assays were carried out in the clinical laboratory of Day General Hospital, Tehran, Iran. Functional fibrinogen level was measured by the Clauss method.[19] D-dimer level was measured with a Tina-quant D-dimer diagnostic kit (Roche, Mannheim, Germany) by particle-enhanced immunoturbidimetric assay with the aid of an automated chemical analysis system (model 704, Hitachi, Tokyo, Japan). Intra- and inter-assay coefficients of variance of this test were 6.6 and 1.1%, respectively. In order to calculate DDFR, the equation below was used:

$$\text{DDFR} = \frac{\text{D-dimer (µg/ml)}}{\text{Fibrinogen (mg/dl)}} \times 100$$

The study was pre-evaluated and approved by the ethics committee of the Iran University of Medical Sciences. All patients or their next of kin were aware of their presence in the study and verbal or written consent was given. All patients participated anonymously and their personal information was kept confidential.

Statistical analysis

All data were entered and analysed by SPSS for Windows version 16. Qualitative data were expressed as percentages and quantitative data as means ± SD. Before the analysis, all data of quantitative variables were tested for normal distribution using the Kolmogorov–Smirnov test. Statistical tests such as the Student's *t*-test, Chi-square and Mann–Whitney *U*-test were used. For calculating the sensitivity and specificity of various cut-off points for D-dimer and DDFR levels in this study, a receiver operating characteristics (ROC) analysis and curve was conducted. In addition, regression analysis was performed to create a model to evaluate the risk factors as a predictive test. A p-value < 0.05 was considered statistically significant.

Results

Baseline characteristics

After excluding 10 patients who did not meet our inclusion criteria, 81 patients were included in this study; 38 males and 43 females. Mean age was 61.62 ± 17.40 years and the mean duration of hospitalisation was 16.78 ± 12.1 days. The most common cause of admission was cardiovascular disorders (23 patients, 28.3%), pulmonary disease (21 patients, 25.9%) and neurologic disorders (12 patients, 14.8%). Other causes such as kidney disease, gastrointestinal bleeding and complications after orthopaedic surgery were seen in the remaining cases (24 patients, 29.6%).

In their medical history, 27 patients (33.3%) had diabetes mellitus (DM), 27 (33.3%) had a history of previous cardiac events (myocardial infarction, unstable angina and other cardiac problems), 40 (49.5%) had hypertension (HTN), and 20 patients (24.7%) had a history of any kind of surgery in the past three months.

At the end of the study, 41 patients (50.61%) were diagnosed as definite PTE cases and 40 (49.39%) had a diagnosis other than PTE and were considered our control group. From the Chi-square test, a significant difference was seen between gender percentages in the PTE and non-PTE groups, as 11 of the 41 (26.8%) PTE-positive patients were males, compared to 23 of 40 (56%) in the PTE-negative group (p = 0.001). Other characteristics are shown in Table 1.

TABLE 1. BASELINE CHARACTERISTICS OF THE PATIENTS INCLUDED IN THE STUDY, DIVIDED BY PATIENTS WITH AND WITHOUT PTE

	All patients (n = 81)	*With PTE (n = 41)*	*Without PTE (n = 40)*	p
Age (years)	61.62 ± 17.40	60.41 ± 14.85	61.85 ± 20.20	0.867#
Duration of hospitalisation (days)	16.78 ± 12.10	14.95 ± 11.65	19.05 ± 12.24	0.154#
CRP (mg/l)	24.65 ± 16.64	21.42 ± 18.00	27.11 ± 14.22	0.921#
Temperature (°C)	37.21 ± 0.62	36.98 ± 0.39	37.46 ± 0.75	0.091#
Systolic BP* (mmHg)	136.21 ± 24.96	136.60 ± 23.80	136.81 ± 26.92	0.980#
Diastolic BP* (mmHg)	83.81 ± 15.01	82.40 ± 16.79	85.56 ± 12.70	0.538#
Heart rate (/min)	88.47 ± 17.21	91.06 ± 16.36	85.56 ± 18.19	0.361#
Respiratory rate (/min)	22.36 ± 6.72	22.94 ± 7.22	21.67 ± 6.24	0.595#
Sodium (mEq/l)	139.36 ± 6.78	141.00 ± 7.36	137.58 ± 5.88	0.201#
Potassium (mEq/l)	4.36 ± 0.54	4.21 ± 0.50	4.54 ± 0.55	0.211$
WBC (/mm^3)	11.07 ± 4.26	3.95 ± 1.02	4.22 ± 1.09	0.073#
Haematocrit (%)	37.00 ± 7.81	36.28 ± 7.49	37.77 ± 6.18	0.565#
pH	7.07 ± 0.76	6.84 ± 0.96	7.39 ± 0.06	0.343$
PO_2 (mmHg)	72.63 ±22.68	64.73 ± 22.50	79.41 ± 21.54	0.258#
PCO_2 (mmHg)	45.38 ± 17.99	47.76 ± 20.69	43.34 ± 16.74	0.684#
HCO_3 (mEq/l)	27.15 ± 10.37	27.05 ± 7.69	27.25 ± 13.33	0.975#

*Blood pressure.
#From independent samples *t*-test (for normally distributed variables).
$From Mann–Whitney U-test (for non-normally distributed variables).

TABLE 2. CONCENTRATION OF D-DIMER, FIBRINOGEN AND DDFR IN PATIENTS WITH AND WITHOUT PTE; BOLD *P*-VALUES ARE SIGNIFICANT

	D-dimer (μg/ml)	*Fibrinogen (mg/dl)*	*DDFR[#] (× 10⁻³)*
PTE positive	4.65 ± 3.46	536.73 ± 186.32	9.13 ± 7.16
PTE negative	2.25 ± 2.55	586.33 ± 211.06	4.83 ± 4.40
*p**	0.006	**0.298**	**0.003**

*From independent samples *t*-test.
[#]D-dimer:fibrinogen ratio.

Mean C-reactive protein (CRP) level was 24.65 ± 16.64 mg/l and white blood cell count (WBC) was 11.11 ± 4.12 /mm³. As shown in Table 1, none of the other parameters had significant differences between patients with and without PTE.

D-dimer, fibrinogen and DDFR

The mean values of D-dimer and fibrinogen levels were 3.99 ± 3.19 μg/ml and 571.4 ± 196.1 mg/dl, respectively. Mean DDFR was 0.712 ± 0.643 × 10^{-3}. As shown in Table 2, D-dimer and DDFR were significantly different between the PTE and non-PTE groups, but the fibrinogen level did not differ significantly.

In order to find the best cut-off points for D-dimer, fibrinogen and DDFR as diagnostic tests for PTE, a ROC analysis was performed. The ROC curve is used to calculate the area under the curve (AUC) as a measure of the diagnostic accuracy. Based on this analysis, for DDFR (AUC = 0.713, $p = 0.003$) a value of 0.105 × 10^{-3} was 100% sensitive and 1.621 × 10^{-3} was 100% specific for a diagnosis of PTE. Furthermore, this analysis on D-dimer values (AUC = 0.721, $p = 0.002$) showed a 100% sensitivity for 0.43 μg/ml and a 100% specificity for 11.5 μg/ml for the diagnosis of PTE. The same analysis on fibrinogen did not show any significant cut-off point (AUC = 0.410, $p = 0.198$) (Table 3, Fig. 1).

Multiple logistic regression analysis was used to create a model to predict the risk for PTE using the significantly different independent variable studied at the level of $p < 0.1$. DDFR, gender, temperature and WBC were included in backward stepwise regression analysis. The first model chosen was the best statistically ($p = 0.029$, $R^2 = 0.577$). The results are shown in Table 4.

Discussion

No significant difference was found in arterial blood gas and complete blood count analysis between the hospitalised PTE and non-PTE patients. These results confirm other studies that showed arterial blood gas or its combination with other data could not be used to detect PTE, and if used alone, may lower the sensitivity and specificity.[20,21]

Fibrinogen (factor I) is a soluble plasma glycoprotein, synthesised by the liver and converted by thrombin into fibrin during blood coagulation.[22] Fibrinogen may increase in acute and chronic conditions as an acute-phase reactant with the same signs and symptoms as PTE. There are few studies on the relationship between fibrinogen level and PTE. A study by Palla *et al.* showed that fibrinogen levels in PTE patients (498 ± 369 mg/dl) were similar to those without PTE (520 ± 268 mg/dl) ($p = 0.29.23$). These results are similar to our results, which demonstrated no significant difference between fibrinogen levels in the PTE and non-PTE patients. However, Kucher *et al*. showed that fibrinogen levels were significantly lower in patients with PTE ($p < 0.0001$).[9]

There is controversy about using fibrinogen levels as a reliable diagnostic test and it should not be used alone in order to diagnose PTE. In addition, the fibrinogen level is unpredictable. It can rise due to acute phases in the ICU or decrease in liver congestion due to right ventricular failure.

In recent years, several studies have been conducted to evaluate the accuracy of a diagnostic test to detect acute PTE in emergency settings. Most demonstrated that D-dimer tests with cut-off points near 0.5 μg/ml could be used as an exclusion test.[9,23-25] As our study showed, D-dimer levels less than 0.43 μg/ml had a 100% sensitivity and a negative predictive value for ruling out PTE. This confirms data from various studies demonstrating the ability of D-dimer to rule out PTE.

The only study that evaluated the D-dimer:fibrinogen ratio in PTE was conducted by Kucher *et al*.[9] They found that a ratio above 1.04 × 10^{-3} had 100% specificity and 57.6% sensitivity for PTE and a two-fold diagnostic rate compared to D-dimer alone, with a cut-off point of 7 μg/ml with 100% specificity and 29.4% sensitivity (57.6% vs 29.4%).[9] A recent study however contradicted Kucher and co-workers' results.

Calvo-Romero's study did not reveal a lower fibrinogen level in PTE patients with a positive D-dimer level, although it

TABLE 3. RESULTS FROM ROC ANALYSIS; BOLD NUMBERS REPRESENT THE BEST VALUE BETWEEN ALL CUT-OFF POINTS CALCULATED FROM THE ROC CURVE

		Sensitivity (%)	*Specificity (%)*	*Positive predictive value (%)*	*Negative predictive value (%)*	*Positive likelihood ratio*	*Negative likelihood ratio*	*Accuracy[$] (%)*
D-dimer (μg/ml)	Best sensitivity (0.43)	**100**	6.9	54.1	100	1.07	-	55.7
	Best accuracy (2.43)	70.3	70.1	72.2	67.6	2.35	0.42	**70**
	Previously used[#] (7.0)	24.1	91.9	75	51.9	2.97	0.82	55.7
	Best specificity (11.5)	5.4	**100**	100	51.4	-	0.84	52.8
DDFR* (× 10^{-3})	Best sensitivity (.105)	**100**	22.2	58.73	100	1.2	-	62.8
	Best accuracy (.233)	91.9	40.4	62.9	81.2	1.54	0.2	**67.1**
	Previously used[#] (1.0)	35.1	84.5	72.2	53.8	2.26	0.76	58.5
	Best specificity (1.32)	18.9	**100**	100	51.6	-	0.81	57.1

*D-dimer:fibrinogen ratio.
[#]The nearest cut-off points in our ROC analysis to the cut-off points used before in other articles and medical references.
[$]Calculated by: Accuracy (%) = $\frac{\text{true positive + true negative}}{\text{total patients}} \times 100$

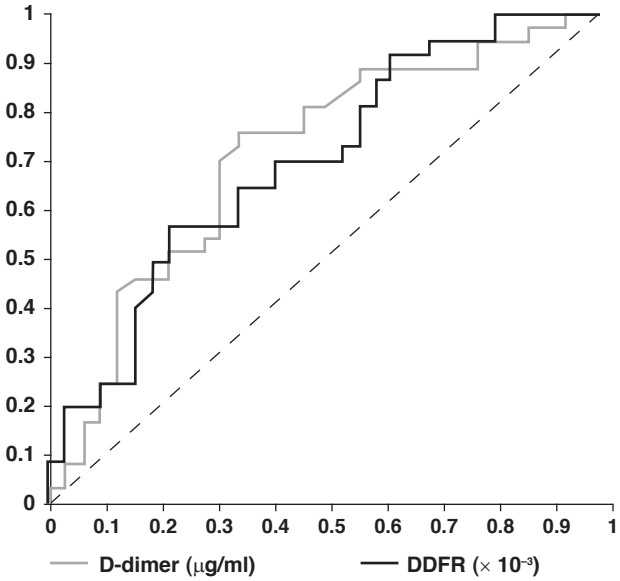

Fig. 1. ROC curve for D-dimer and DDFR to diagnose PTE by different cut-off points; compare with Table 3.

showed the D-dimer test to be less sensitive (semi-quantitative latex agglutination D-dimer assay with 78% sensitivity). It also demonstrated that patients with PTE had fibrinogen levels within the normal range (200–400 mg/dl). However, the sample size of the study was small compared to other studies in this field (40 cases).[26]

The aim of our study was to determine whether there was an inverse relationship between D-dimer and fibrinogen levels. The theory was that while the activation of the coagulation cascade consumes fibrinogen in the pulmonary vasculature to form fibrin, the activation of fibrinolysis results in elevated fibrin degradation products such as D-dimer.[9] This theory may be applicable in acute PTE without complications and for any other factor that may influence D-dimer and fibrinogen (as an acute-phase reactant) concentrations in out-patients. In patients with other complications, these biomarkers will be different.[11-15]

We hypothesised that the conditions influencing D-dimer and fibrinogen levels would magnify the difference between these biomarkers when combined, and therefore lead to a more accurate diagnosis. As our study shows, when using the same cut-off points that Kucher *et al*. presented, D-dimer > 7 μg/ml was 24% sensitive and 91.9% specific, and DDFR > 10^{-3} was 35.1% sensitive and 84.5% specific. Based on our study, D-dimer > 2.43 μg/ml and DDFR > 0.233 × 10^{-3} had the best accuracy (70 and 67.1%, respectively). However neither was accurate enough to be used alone for the diagnosis of PTE in the ICU setting or in long-term hospitalised patients suspected of having PTE.

Study limitations

Up to the end of the first phase of our study, 91 patients were enrolled and after filtering by the exclusion criteria, 81 patients were included. Due to the use of antithrombotic agents and good medical care, the incidence of PTE was low in the two hospitals where we collected the samples. Therefore we could not divide the patients into groups with different setting, such as medical ICU and surgical ICU, in order to evaluate the influence of different settings on D-dimer level and DDFR. We recommend a study to compare fibrinogen and D-dimer levels and DDFR in different settings and also in emergency departments as a unique study to make the comparison more reliable.

TABLE 4. RESULTS OF LOGISTIC REGRESSION ANALYSIS OF SIGNIFICANTLY DIFFERENT INDEPENDENT VARIABLES AT THE LEVEL OF < 0.1, BOLD P-VALUE IS CONSIDERED SIGNIFICANT

	p	*Odds ratio*	*95% CI*[$]
DDFR (× 10^{-3})*	**0.025**	1.72	1.442–2.113
WBC (/mm^3)[#]	0.373	1.11	0.875–1.454
Temperature	**0.001**	145	0.542–3.91 E3
Gender	**0.05**	0.76	0.003–2.12

*D-dimer:fibrinogen ratio.
[#]White blood cell count.
[$]95% confidence interval calculated.

Conclusion

No significant difference was found in the biochemical assays between the hospitalised PTE and non-PTE patients. Moreover, the significant difference in DDFR originated from D-dimer and not fibrinogen levels. Therefore DDFR appears to be almost as useful as D-dimer in diagnosing PTE in the ICU setting. In addition, it was possible to rule out PTE with only the D-dimer cut-off value of < 0.43 μg/ml without using DDFR. However, neither of these evaluations could replace angiography or CT angiography.

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Cardiovascular congress diary

Date	Place	Conference	Contact details to register
SEPTEMBER 2012			
29 September	Trend 2012 Asia–Pacific	Hong Kong	www.csi-trend.org
29 September – 4 October	24th International Society of Hypertension, annual scientific meeting	Sydney, Australia	www.ish2012.org
OCTOBER 2012			
4–7 October	13th national congress of cardiology	Sofia, Bulgaria	http://www.cim.bg/index.php/en/view/xiii-national-congress-cardiology
5 October	New Horizons in Echocardiography	Sandton, South Africa	baraecho@gmail.com
10–13 October	8th World Stroke congress	Brasilia, Brazil	www.2.kenes.com/stroke/pages/home.aspx
20 October	The Many Faces of AF symposium	Cape Town, South Africa	franciska@cassa.co.za
20–22 October	Acute Cardiac Care	Istanbul, Turkey	www.escardio.org
24 October	The Many Faces of AF symposium	Durban, South Africa	franciska@cassa.co.za
27 October	The Many Faces of AF symposium	Johannesburg, South Africa	franciska@cassa.co.za
NOVEMBER 2012			
3–7 November	American Heart Association scientific sessions	Los Angeles, US	www.americanheart.org
14–16 November	2nd international joint meeting on thoracic surgery 2012	Barcelona, Spain	http://thoracicsurgery2012.org/
16–17 November	LAA 2012	Frankfurt, Germany	www.csi-laa.org
18–19 November	Europe Atrial Fibrillation 2012	London, UK	www.europeaf.com
DECEMBER 2012			
5-8 December	The 16th annual EUROECHO and other imaging modalities	Athens, Greece	www.euroecho.org
FEBRUARY 2013			
31 January – 3 February	2nd international conference on prehypertension and the cardio-metabolic syndrome	Barcelona, Spain	www.prehypertension.org
6–8 February	8th international Stroke Conference and the Nursing Symposium 2013 (ISC)	Honolulu, Hawaii, USA	http://my.americanheart.org/professional/Sessions/InternationalStrokeConference
10–15 February	Cardiology Update 2013, 20th international postgraduate course on cardiovascular disease	Davos, Switzerland	www.escardio.org
22 February – 2 March	15th Cardiology and Diabetes at the Limits 2013	Cape Town, SA	www.atthelimits.org
27 February – 1 March	5th world symposium on pulmonary hypertension	Nice, France	www.wsph2013.com/

Role of four-week resistance exercise in preserving the heart against ischaemia–reperfusion-induced injury

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Abstract

Objective: **We studied the cardioprotective effect of resistance training against ischaemia–reperfusion-induced injury.**

Methods: **Forty male rats were divided into trained and sedentary groups (n = 20 for each). The trained rats were exercised at 12 repetitions/set, four sets/day and five days/week for four weeks. Transient regional ischaemia of the left anterior descending coronary artery (40 min) was followed by 80 min of reperfusion.**

Results: **Baseline developed and diastolic pressures and coronary flow were similar in the two groups. While diastolic pressure increased and developed pressure and coronary flow decreased in both the ischaemic and perfusion periods (as indices of cardiac damage), there were no statistically significant differences between the trained and sedentary groups in these parameters. Resistance training did not significantly change the infarct size and apoptosis rate.**

Conclusion: **We did not see a cardioprotective effect of resistance exercise against ischaemia–reperfusion-induced injury in this study. A precise conclusion about this issue needs more investigations.**

Keywords: exercise, heart, infarction, ischaemia, reperfusion

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Ischaemic heart disease remains a worldwide problem affecting all economic groups of society.[1] The primary pathological manifestation of ischaemic heart disease is myocardial infarction due to ischemia–reperfusion (IR) injury.[2] Preservation of cardiac performance and reduction of infarct size are the main goals in the management of IR-induced complications.[2] In this regard, many approaches to providing cardioprotection against IR-induced injury have been studied.

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Until now, regular exercise has been confirmed as a pragmatic and sustainable countermeasure for cardioprotection.[3] While convincing evidence indicates that both short-term (three to five consecutive days) and long-term (months) endurance exercise training (i.e. running and swimming) improves myocardial tolerance to IR-induced injury in both male and female animals as well as young and old animals,[3] there is no clear understanding of the cardioprotective effect of resistance exercise training (such as body building and weight lifting) against IR-induced injury.

Resistance exercise training is a specialised method of conditioning designed to increase strength and muscle endurance.[4] Similar to endurance training, it has been shown that resistance training has beneficial effects on some physiological and pathological processes such as physical fitness, quality of life and chronic heart failure.[5] While the risk of cardiovascular complications is the primary concern with resistance training in some cardiac patients (due to blood pressure elevation during this type of exercise), resistance training can positively influence quality of life, cardiovascular risk factors and cardiovascular function in healthy persons and in selected patients with cardiovascular disease.[5,6]

Although several investigators have studied the impact of resistance training on cardiac structure and function, the cardioprotective effect of resistance exercise training against IR-induced injury has not been understood. The purpose of this study was to investigate cardiac performance during the ischaemic and reperfusion periods, as well as to determine cardiac infarct size and apoptosis rate after IR-induced injury in rats undergoing resistance exercise training for a short period of four weeks.

Methods

Forty male Wistar rats (220–240 g, three months old) were obtained from the laboratory animal house of Tabriz University of Medical Sciences and they were randomly divided into trained (EXT) and sedentary (Sed) groups (n = 20 for each group). Animals were housed at room temperature (23 ± 1°C) with 12-hour light/dark cycles and had free access to food and water. The study protocol was designed in accordance with the *Guide for the Care and Use of Laboratory Animals* published by the US National Institutes of Health (NIH publication, revised 1996) and approved by the Ethics Committee for the Use of Animals in Research of the Tabriz University of Medical Sciences.

Trained rats were exercised according to the model described by Tamaki *et al*., with some modifications.[7] Rats were placed vertically in a squat-training apparatus cylinder (RatWLI009, Tajhiz Azmaye Pooya Co, Iran) as they could stand on their hind limbs in response to electrical stimulation and raise the piston which was located above their heads. An electrical stimulation (20 V, 0.3-s duration at 3-s intervals) was applied to the rat's tail through a surface electrode. After one week of adaptation, the trained group of rats exercised for four sets of 12 repetitions per

day, with a 90-s rest period between each set, five times per week for four weeks.[4]

Each rat in the trained group was weighed daily and 120% of its body weight (approximately 70% of the maximum load that the rats were able to raise following electrical stimulation) was used to determine the weight of the piston. The piston movement for each rat was recorded by a distance sensor which had been located above the piston and the work performed by each rat was calculated daily by multiplying the piston weight and piston movement.

According to the method of Brown *et al*., after anaesthetisation with pentobarbital sodium (35 mg/kg ip injection) the hearts were excised, placed in ice-cold saline and rapidly hung by the aorta on the cannula of the Langendorff apparatus.[8] Hearts were perfused with 37.5°C Krebs buffer (76.5 mmHg perfusion pressure with 95% O_2 and 5% CO_2) containing 117.4 mM NaCl, 4.7 mM KCl, 1.9 mM $CaCl_2$, 1.2 mM $MgSO_4$, 1.2 mM KH_2PO_4, 5 mM pyruvate, 11 mM glucose, 0.5 mM EDTA, 25 mM $NaHCO_3$ and 1200 U/l heparin.

A pressure-transducing catheter was placed through the cannula and aortic valve into the chamber of the left ventricle (LV) and the developed pressure was determined with a computer connected to the transducer (PowerLab, AD Instruments, Australia). After a 5-min stabilisation period, baseline pressure was measured, and coronary flow rate was obtained by collection of the coronary effluent for 1 min.

After baseline records, a suture was threaded through the left anterior descending coronary artery 3–5 mm distal to the aorta in 14 rats in each group. Both ends of the suture were inserted into a small polyethylene tube that was used as a snare, and ischaemia was induced by tightening the snare so that the artery was fully compressed. Pressure and coronary flow measurements were recorded at 5, 15, and 30 min after the onset of ischaemia. After 40 min, the snare was loosened and reperfusion ensued for 80 min. Coronary flow and pressure data were recorded at 5 min after the onset of reperfusion and then every 15 min until the end of the 80-min reperfusion period.

Data were omitted from analysis if the coronary flow did not decrease at the onset of ischaemia or increase at the onset of reperfusion (n = 3), or if the hearts did not complete the IR protocol due to fibrillation or technical difficulty (n = 2). Only 11 hearts in the control group and 12 in the trained group completed the IR protocol.

In the remaining rats from each group (n = 6), the hearts were excised, cannulated and perfused as described above but without the ischaemic period, to observe how the mechanical and flow measurements changed as a function of time. Pressure and flow were recorded in these hearts at the same time points as in the hearts that experienced ischaemia–reperfusion.

Infarct size was measured using methods similar to those previously described.[8,9] After the reperfusion period, the snare was re-tightened around the left anterior descending coronary artery in six hearts from each group, and 100 µl of 0.05% Evans blue solution was injected into the aortic cannula and perfused through the heart for 3 min. Then the heart was sliced transversely from base to apex into four slices of equal width. Each slice was immersed in phosphate buffer and was photographed with a digital camera.

After both sides of each slice were photographed, each slice was placed in 100 mM phosphate buffer with 0.1% triphenyltetrazolium chloride and incubated for 10 min at 37°C. After incubation, each side of every slice was again photographed and the slices were weighed. Heart weight was obtained by summation of the slice weights for each heart.

To avoid experimenter bias, images of the slices were analysed in a single-blind manner by Scion Image 4.0 software. Total slice area (TA), zone at risk (ZAR: the area of each slice that did not turn blue after perfusion with the solution containing Evans blue dye) and infarct area (IA: the portion of the ZAR that did not turn red in response to triphenyltetrazolium chloride incubation and remained white) were measured. ZAR and IA were obtained from each side of a single slice, and the mean of both sides was used as the representative ZAR and IA for that slice. Finally, IA was expressed as a fraction of all ZAR by taking the sum of all infarcts and was reported as a percentage.

The left ventricle was immersion-fixed in 10% neutral formalin and embedded in paraffin wax (n = 5 for controls, n = 6 for exercised rats). Serial sections of 4-µm thicknesses were prepared. Apoptosis was evaluated via the terminal deoxynucleotidyl transferase-mediated dUTP nick-end labelling (TUNEL) method with the use of an *in situ* Cell Death Detection Kit, POD (1684817, Roche, Germany) according to manufacturer's instructions, with some modifications.[10]

Briefly, the tissue sections were dewaxed and rehydrated by heating at 60°C, followed by washing in xylene and rehydration through a graded series of ethanol and double distillated water. Then the sections were incubated for 30 min at 21–37°C with proteinase K working solution (20 µg/ml in 10 mM Tris-Cl, pH 7.6). The sections were rinsed with PBS and incubated with the TUNEL reaction mixture for 1 h at 37°C in a humidified chamber.

As a positive control, sections were treated with DNase I (1 mg/ml, Sigma) for 10 min to introduce nicks in the genomic DNA. After converter peroxidase (POD) was added, the sections were incubated for 30 min at 37°C in a humidified chamber. Then the 3,3-diaminobenzidine substrate was added for the visualisation of nuclei with DNA nick-end labelling. The sections were counter-stained with toluidine blue to show normal nuclei.

The percentage of myocytes with DNA nick-end labelling was analysed by counting the cells exhibiting brown nuclei at × 40 magnification in five randomly chosen fields (1 mm^2) in triplicate plates. The number of TUNEL-positive cardiomyocytes was counted by double-blinded observation.

Statistical analysis

All statistical comparisons were made using SPSS 16.0 software (Chicago, IL) and were expressed as means ± SD. Work performed, pressures and flow data were analysed using repeated measures ANOVA. When a significant p-value was obtained, a *post hoc* Bonferroni test was used to determine the differences between the groups. Between-group comparisons of data of heart rate, infarct size, body weight, heart weight and apoptosis rate were made using the Student's t-test. A p-value of < 0.05 was considered statistically significant.

Results

Morphological data from the EXT and Sed rats are presented in Table 1. The rats in the EXT group had significantly lower body weights and higher heart weights than the Sed group (p

TABLE1. EFFECTS OF RESISTANCE EXERCISE ON THE RAT MORPHOLOGY

	Sed	*EXT*
Body weight (g)	266 ± 13	259 ± 11
Heart weight (g)	0.75 ± 0.06	0.84 ± 0.06**
Body:heart ratio	2.8 ± 0.15	3.2 ± 0.18**

Values are mean ± SD (n = 10 rats); **$p < 0.05$, significantly different from the sedentary group; Sed: sedentary and EXT: exercise-trained rats.

< 0.05). In addition, heart-to-body weight ratio, as an index of heart hypertrophy, was greater in the EXT rats than the sedentary ones ($p < 0.05$).

Fig. 1 shows a progressive increase in the weight-lifting ability of the EXT rats. Both the Sed and EXT groups had similar values for work performed in the first (week 1) of the protocol. The work performed at the end of weeks 2, 3 and 4 were significantly higher in the EXT rats than the Sed group ($p < 0.05$, $p < 0.01$ and $p < 0.01$, respectively) and their previous week's values ($p < 0.05$, $p < 0.05$ and $p < 0.01$, respectively).

Developed pressure, diastolic pressure and coronary flow changes during the time-control and ischaemia–reperfusion periods for the EXT and Sed groups are shown in Fig. 2. Baseline coronary flow, developed pressure and diastolic pressure were similar in the two groups. No between-group differences in developed or diastolic pressure were observed at any time point in the non-ischaemic time-control measurements. While diastolic pressure increased and developed pressure and coronary flow decreased in both the ischaemia and reperfusion periods (as indices of cardiac damage), there were no statistically significant differences between the EXT and Sed groups in these parameters.

Figs 3 and 4 show the size of the infarction and the apoptosis rate, respectively in the hearts of the EXT and Sed groups. Resistance exercise training did not significantly change the infarct size or apoptosis rate.

Discussion

Our previous study showed that 12-week resistance exercise training preserved the heart against IR-induced injury.[11] Although there are some reports on the effect of resistance training on cardiac structure and function, to the best of our knowledge, this is the first study that has focused on the role of short-term resistance training in preserving the heart against IR-induced

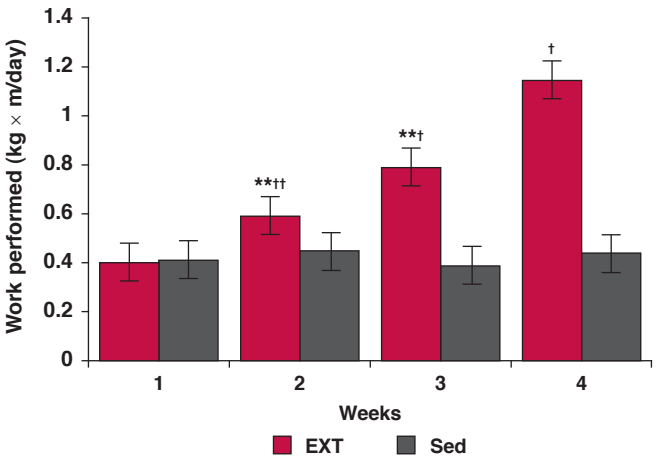

Fig. 1. Work performed by rats after the end of each week of resistance exercise training. Values are mean ± SD (n = 20 rats); *$p < 0.01$, **$p < 0.05$ compared with previous week; †$p < 0.01$, ††$p < 0.05$ compared with the sedentary group; Sed: sedentary and EXT: exercise-trained rats.

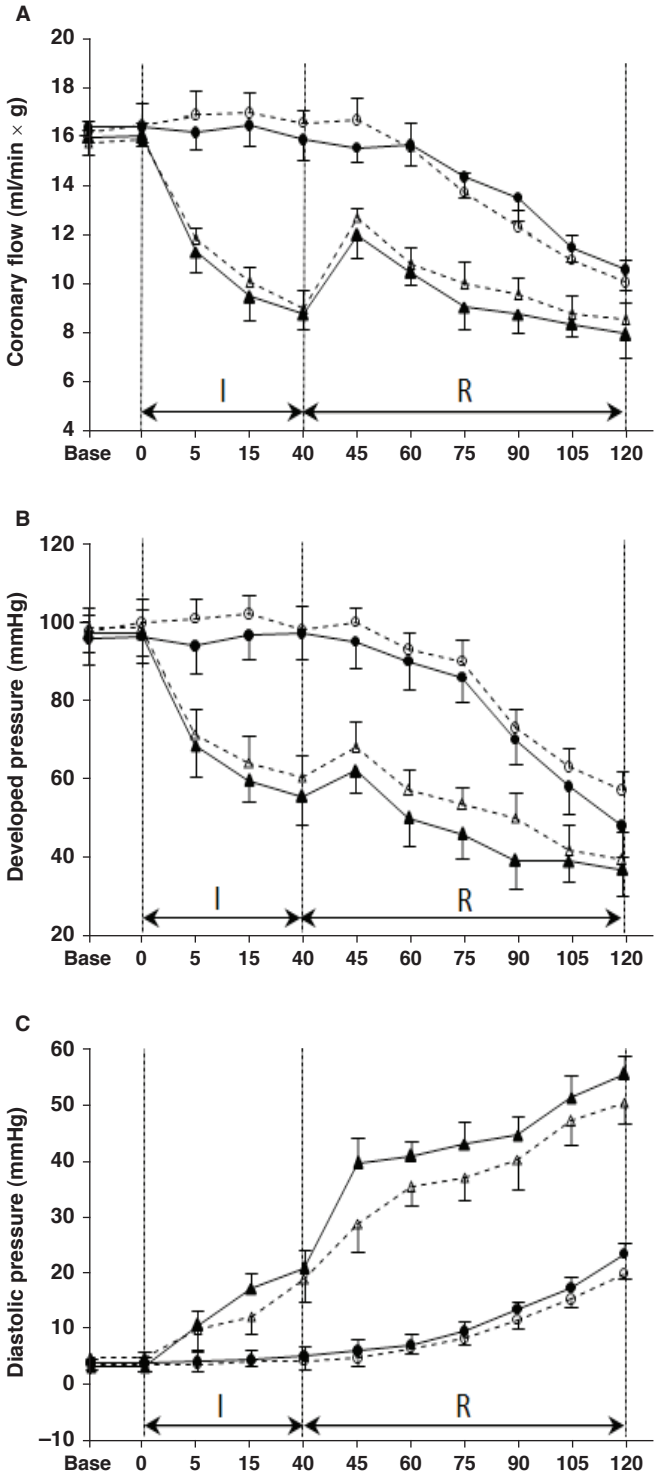

Fig. 2. Haemodynamic indices of the heart during non-ischaemic time control (○ exercised and ● sedentary rats; n = 6 for each), regional ischaemia (I) and subsequent reperfusion (R) (Δ exercised and ▲ sedentary rats; n = 12 for trained and n = 11 for sedentary animals). A: diastolic pressure. B: Left ventricular developed pressure (LVDP). C: Coronary flow. Values are mean ± SD.

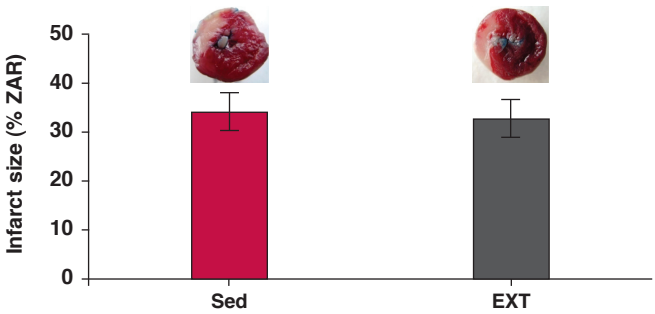

Fig. 3. Effect of resistance exercise on the heart infarct size. Top: representative digital images of the stained heart. Non-necrotic viable tissue is dark, and infracted tissue is light. Bottom: quantification of average infarct size expressed as a percentage of ischaemic ZAR (zone at risk). Values are mean ± SD (*n* = 6 rats); Sed: sedentary and EXT: exercise-trained rats.

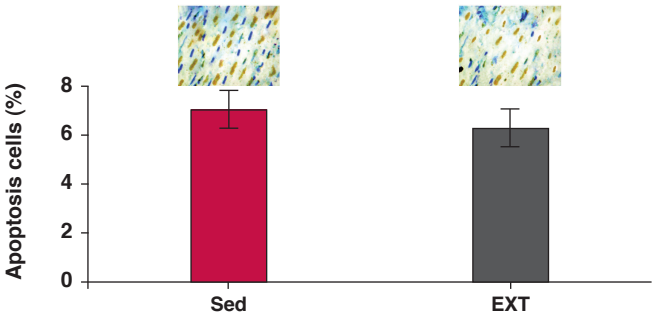

Fig. 4. Effect of resistance exercise on the heart apoptosis rate. Top: cell death determined by the TUNEL method at × 40 magnification (black nuclei are the apoptotic cells). Bottom: comparison of apoptotic cell ratios in the two groups. Sed: sedentary and EXT: exercise trained rats. Values are mean ± SD (▲ = 6 for trained and ▲ = 5 for sedentary rats).

injury.

The main findings of the present study were that four weeks of resistance training: (1) increased the weight-lifting ability, (2) induced cardiac hypertrophy without any significant change in cardiac function, and (3) did not preserve the heart against IR-induced injuries, as evidenced by no change in the infarct size and apoptosis rate.

Weight loss, cardiac hypertrophy and work performed are some of the indices to characterise training efficiency. Previously, Barauna *et al*. reported that four weeks of resistance training in rats increased their weight-lifting ability and induced cardiac hypertrophy with no change in cardiac function.[4] Progression in weight-lifting ability indicates training efficacy and development. While maximum heart rate or VO_{2max} are used to prescribe endurance exercise training,[5] work performed may be a good indicator of resistance-training efficacy. Moritany and Vries showed that neuronal and muscular adaptations were involved in training-induced enhancement of the rat's muscular strength.[12]

Resistance training is a known stimulus for cardiac hypertrophy due to pressure overload imposed on the heart during training.[13] Our results are in agreement with pervious research.[4,13] The precise underlying mechanism of resistance training-induced cardiac hypertrophy needs to be elucidated. In this regard it has been suggested that induction of angiotensin receptor type 1 (AT_1) expression in the heart and elevation of circulating anabolic hormones may be involved.[13,14]

In this study, coronary flow, left ventricular developed pressure and diastolic pressure did not differ significantly between the trained and untrained rats. There are several published reports on the beneficial effect of resistance exercise on cardiac performance in patients with heart failure.[15-17] In this regard it has been proposed that resistance training could improve stroke volume and ejection fraction without enhancement of cardiomegaly or cardiac deterioration.[15-17]

Few studies have investigated the effect of this type of exercise on cardiac function in healthy individuals and most did not report on changes in heart function after resistance training.[18-20] Moreover, Barauna *et al*. reported that four weeks of resistance training did not change cardiac function in rats. Our results are in agreement with the results of these studies.[4]

Growing evidence indicates that IR-induced myocardial cell death is not limited to necrosis but also includes apoptotic cell death.[21] For this reason, we measured ventricular apoptosis rate and infarct size in our study. The results show that short-term resistance training neither induces excessive damage to the heart nor preserves it against IR-induced injury, because apoptosis rate and infarct size did not change between our trained and control animal hearts.

While it has been shown that short- to long-term endurance exercise can protect the heart against IR-induced injury,[3] some investigations did not report the beneficial effects of endurance exercise (up to 12 weeks) on cardiac performance, anti-oxidant defense and cell death rate.[10,22] It has been proposed that these controversial results could have resulted from methological differences, such as type and duration of endurance exercise (swimming, treadmill or wheel running), time between the end of the training programme and sacrifice of the animals.[23]

Conclusion

Previously we saw that 12-week resistance exercise training preserved the heart against IR-induced injury but the results of this study showed that four-week resistance training was unable to achieve this. Nevertheless, this is the first study with this purpose and a precise conclusion about this issue needs more investigation.

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The effect of the first office blood pressure reading on hypertension-related clinical decisions

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Abstract

The effect of the first office blood pressure reading (FBPR) on hypertension-related decisions was evaluated using blood pressure (BP) readings taken with the BpTRU BPM-100 device. BP readings were grouped into three pairs: (1) single readings (first and second readings), (2) computed average of three readings (one including and one excluding the first reading), and (3) computed average of five readings (one including and one excluding the first reading). Categorisation of BP readings under JNC-7 classes and distribution into < 140/90 and ≥ 140/90 mmHg groups were selected as parameters guiding hypertension-related decisions. Readings including FBPR had strong positive correlations to those excluding FBPR (Pearson's correlation coefficient ranged from 0.86–1.00). Also, FBPR-included and FBPR-excluded readings did not differ statistically in JNC-7 categorisation or distribution into < 140/90 or ≥ 140/90 mmHg groups. Our findings suggest that exclusion of FBPR may have no significant impact on hypertension-related clinical decisions.

Keywords: first BP reading, hypertension, clinical decisions

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Issues regarding the validity and reliability of office blood pressure (OBP) readings have challenged the prime role hitherto played by OBP measurements in the management of hypertension. The white-coat effect, masked hypertension and various observer biases are the chief factors compromising the usefulness of OBP readings.[1] The result has been a shift to the use of 'out of office measurements' such as home blood pressure measurements (HBPM) and ambulatory blood pressure measurements (ABPM) as more reliable assessors of blood pressure (BP).[2] HBPM has also been shown to be a better predictor of cardiovascular risk than OBP.[3]

The wide applicability of ABPM is greatly limited by the high cost of this technology. At present, it is not feasible to have all patients conduct HBPM prior to hospital visits, especially among resource-poor populations. HBPM is challenging for the visually impaired and the elderly with psychomotor impairments. The diversity in the design of devices used in HBPM and variability in their algorithms and outputs continue to give cause for concern. There will be a continued need for clinicians to conduct OBP measurements. Therefore efforts geared towards the improvement of the validity and reliability of OBP measurements would be invaluable.

For clinical decisions, most guidelines recommend the use of average BP values derived from multiple readings. This is to achieve a closer approximation of BP readings to the patient's true BP by compensating for the intrinsic physiological variability of BP with each heart beat (the beat-to-beat variation of BP).[4,5] However, the constraints of time and limited availability of trained personnel have sustained the practice of taking a single measurement in the waiting room or the doctor's office. This is particularly common in busy clinics serving resource-deficient settings.

Discarding the first blood pressure reading (FBPR) and using the average of the next two or more readings has also been advanced as a strategy to improve the accuracy of BP readings. One important reason cited for the exclusion of FBPR is the theoretical potential of this strategy to compensate for the 'office pressor effect' – a phenomenon characterised by the recording of a high first BP reading that is followed by lower BP readings.[6] While the beat-to-beat variability of blood pressure and the white-coat phenomenon justify the need for multiple readings and use of mean BP values, the additional benefit of discarding the first reading has not been proven.

Blood pressure-related clinical decisions are based on a synthesis of several clinical parameters. One such is the categorisation of the patient's BP reading on a reference classification system. The BP classification published in the 7th report of the Joint National Committee on the prevention, detection, evaluation and treatment of hypertension (JNC-7 classification) is the most recent and most widely used.[7] The localisation of the blood pressure reading relative to a threshold value (e.g. < 140/90 mmHg for control in patients with uncomplicated hypertension or ≥ 140/90 mmHg for diagnosis of hypertension in the office setting) is another important parameter that influences the clinician's decisions.

Despite being advocated as a beneficial clinical practice, the value of discarding the first blood pressure reading (FBPR) is yet to be determined by research. In this study, we aimed to explore the impact of FBPR on hypertension-related clinical decisions in a general out-patient setting. Our objectives were to evaluate the impact of FBPR on (1) the distribution of participants' BP readings using the JNC-7 classification model and a customised modification, (2) consideration of a diagnosis of hypertension among the previously undiagnosed sub-population of the study sample, (3) clinical assessment of BP control among the previously diagnosed and treated hypertensive sub-group of the participants.

Methods

This descriptive, cross-sectional study was conducted among a selected sample of 186 consenting adults (aged 18 years and over) attending the general out-patients' clinic of the Department

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of Family Medicine, Lagos State University Hospital (LASUTH), Lagos, Nigeria. The general out-patients' clinic is the first contact clinic for all patients presenting at the hospital with non-urgent conditions. The study was approved by the Institution's research ethics committee (LHREC/08/054).

Participants were consecutively recruited in the waiting hall of the clinic, where patients are seated and take their turn to see the nurse for evaluation of vital signs. The study was introduced to each patient by the clinic nurse, who offered each adult the option of having automated blood pressure measurement with the use of a device that could obtain six consecutive readings in a designated office. Associated time required and attendant discomfort from repeated cuff inflation and deflation were explained to prospective participants. Signed informed consent was obtained from all individuals who agreed to participate.

Inclusion criteria were: willingness to voluntarily participate and the absence of any acutely distressful condition such as fever, breathlessness and pain. Patients excluded were those with irregular pulse rhythm or a mid-upper arm circumference greater than 42 cm (oscillometric devices are unreliable in persons with arrhythmias or mid-upper arm circumference > 42 cm), and all patients who had smoked cigarettes or taken coffee on the day of examination.[4]

Blood pressure measurements were conducted in an office devoid of noise or vibrations, offering optimum comfort to the participants. Patients were instructed by a trained research assistant to relax and avoid arm movement during the measurements. The research assistant witnessed and documented the reading obtained from the first measurement, and then left the room. Participants were trained and instructed to remove the cuff and press a door bell, calling for the return of the research assistant after the completion of the six measurements. All measurements were taken with an automated oscillometric blood pressure machine, BpTRU BPM-100 (VSM Medical Technologies, Canada) with strict adherence to the American Heart Association recommendations for clinical BP measurement.[4]

The BpTRU machine uses an oscillometric algorithm for the determination of systolic and diastolic BP. It is designed to take six BP readings with a programmable rest interval between each measurement (resting time between measurements can be set at one, two or three minutes). The interval between measurements has been shown to have no effect on the readings obtained by this device.[8] For this study, the resting time was set at one minute to keep the time committed to the study by each volunteer to the lowest possible, in order to minimise the interference of the study with their primary aim of clinic attendance.

The BpTRU device automatically discards the first reading and computes the average systolic and diastolic BP from the average of the last five readings. All six readings (including the first reading) as well as the computed average are digitally displayed. The device has been validated with the British Hypertension Society (BHS) protocol and passed with an A/A grade.[9]

All the BP readings displayed by the machine were accurately documented. The average readings computed by the device were also recorded. Participants' biodata, history of hypertension/use of antihypertensive medications were also noted. Data collection was concluded on the 186th participant (after six months) due to resource (time, space and personnel) constraints. At this point, it was judged that the sample would suffice for the purpose of the study because adequate representation of hypertensive and non-hypertensive participants had been attained to ensure adequate statistical power for sub-population analysis. The final study sample was separated into two sub-populations, namely, a hypertensive sub-population (individuals with a previous diagnosis of hypertension) and a mixed sub-population comprising normotensive and yet undiagnosed possibly hypertensive individuals.

Three BP measurement models, namely single, triple (average of three consecutive readings) and quintuple (average of five consecutive readings) BP readings were created from the database. We evaluated the effect of inclusion or exclusion of FBPR on: (1) distribution of participants' BP readings in a JNC-7 classification model for the mixed sub-population and a modified JNC-7 classification model (in which the optimal BP and pre-hypertensive domains were merged and relabeled stage 0) for the hypertensive sub-population, (2) consideration of a diagnosis of hypertension among the mixed sub-population of the study sample, and (3) clinical assessment of BP control among the hypertensive sub-population of the participants. The correlations between the readings that included FBPR and those excluding FBPR were also evaluated.

Lastly, differences between the compared readings in each measurement model were evaluated to determine and compare the proportion of differences among the hypertensive and mixed sub-populations respectively, those = 0 mmHg and those ≥ 5 mmHg. (Differences ≥ 5 mmHg are considered clinically significantly different in the British Hypertension Society's protocol for validating BP devices).[10]

Variables used in data analysis included:

- first BP reading (SYS-1 and DIA-1)
- second BP reading (SYS-2 and DIA-2)
- average of three readings, including FBPR: SYS_{1-3} and DIA_{1-3}
- average of three readings, including FBPR: SYS_{2-4} and DIA_{2-4}
- average of five readings, including FBPR: SYS_{1-5} and DIA_{1-5}
- average of five readings, including FBPR: SYS_{2-6} and DIA_{2-6}.

Data redesignation became imperative because of the need for joint consideration of systolic and diastolic values for JNC classification and relativity to the threshold of 140/90 mmHg. SYS_{1-3}/DIA_{1-3}, SYS_{2-4}/DIA_{2-4}, SYS_{1-5}/DIA_{1-5} and SYS_{2-6}/DIA_{2-6} were designated as AVE_{1-3}, AVE_{2-4}, AVE_{1-5} and AVE_{2-6}, respectively. Likewise, SYS-1/DIA-1 and SYS-2/DIA-2 were designated as FBPR and SBPR, respectively. Cases in which systolic and diastolic readings fell under different JNC-7 stages were treated by classifying the BP reading under the higher category, as recommended in the JNC-7 report. This principle was extended to the classification of the BP readings into < 140/90 or ≥ 140/90 mmHg.

Statistical analysis

Data analysis was performed using GraphPad Prisms version 5 for Windows. All study data were first evaluated with descriptive statistics. In addition to the final study sample, sub-groups that included the hypertensive sub-population (those who had been diagnosed as having hypertension) and a mixed sub-population (comprising true normotensives and undiagnosed hypertensives) were identified, analysed and compared.

Correlation statistics and comparison of mean values were performed after evaluation of data for normality. Comparisons

involved the pairs of: FBPR and SBPR, AVE_{1-3} and AVE_{2-4}, and AVE_{1-5} and AVE_{2-6}. Differences in the distribution of compared BP readings under the JNC-7 model for the mixed sub-population and a modified JNC-7 classification model for the hypertensive sub-population were respectively tested for significance using the Chi-square test.

Fisher's exact test was used in evaluating the statistical significance of the differences in the distribution of compared readings under the < 140/90 mmHg and ≥ 140/90 mmHg groups. Correlation between the compared variables was evaluated using Pearson's correlation. For all statistical tests, a p-value < 0.05 was considered statistically significant.

Results

Blood pressure measurements were conducted on 186 consenting adults. Of these, 170 participants (91.4%) had complete sets of the six readings required for data analysis. This was taken as the final study population. This final study sample comprised BP readings from 87 males and 83 females (M:F = 1.05:1), with age range 18–86 years (46.7 ± 13.9).

Patients who had been previously diagnosed as having systemic hypertension comprised 35.9% (n = 61) of the final sample. All had received prescription(s) for antihypertensive medications during previous clinic visits. Females comprised 59% (n = 36) of the hypertensive sub-population and 43% (47 of 109) of the remaining mixed sub-population (p = 0.06, Fisher's exact test). Patients comprising the hypertensive sub-population were older than those in the mixed sub-population [24–86 years (51.3 ± 12.2) vs 18–74 years (44.1 ± 14.2); p = 0.0009, independent t-test].

Table 1 shows the descriptive statistics for the BP variables that were compared in this study. These were presented as range of values (mean ± standard deviation). Within each of the groups in Table 1, the independent t-test found statistically non-significant differences (in respective systolic and diastolic component comparison) between the means of the first and second BP readings, as well as the means of the averages of three readings, and the averages of five readings (p > 0.05 for all).

For the single, triple and quintuple measurement models respectively, systolic/diastolic readings, which included the FBPR, were higher than those that excluded the first reading in 64.2%/58.7%; 78%/68.8%; 82.6%/78.9% of readings among the mixed population. Similarly, corresponding proportions among the hypertensive population were 67.2%/70.5%; 82%/78.7%; 82%/85.2% of the systolic/diastolic readings.

Differences between the sub-populations in the relative proportion of FBPR-included readings which were higher than FBPR-excluded readings were statistically insignificant for both systolic and diastolic comparisons (Chi-square test, p > 0.05 for all). In both sub-populations, it was observed than the tendency to have higher systolic/diastolic readings with the inclusion of FBPR was amplified in the triple and quintuple measurement models.

Conversely, in each of the three measurement models, readings excluding FBPR were greater than those including FBPR in 27.5%/35.8% (single), 9.2%/8.3% (triple), 4.6%/6.4% (quintuple) of the systolic/diastolic readings among the mixed population. Corresponding findings among the hypertensive sub-population were 26.2%/23%; 14.8%/9.8% and 13.1%/6.6%.

Similarly, differences between the sub-populations in the relative proportion of FBPR-excluded readings which were higher than FBPR-included readings were statistically insignificant for both systolic and diastolic comparisons (Chi-square test, p > 0.05 for all). It was also observed than the tendency to have higher systolic/diastolic readings with the exclusion of FBPR was reduced in the triple and quintuple models in both sub-populations.

Table 2 shows the differences (expressed as absolute values) between the compared readings. Readings including FBPR were found to be equal to those excluding FBPR in 8.3–12.8%/5.5–22.9% and 6.6–13.1%/6.6–11.5% of systolic/diastolic readings among the mixed and hypertensive sub-populations, respectively. Differences between the proportions of equal readings in the sub-populations were not statistically significant (p > 0.05 for all). Clinically significant differences (≥ 5 mmHg) were observed between compared systolic/diastolic readings in 18.3–56.9%/0.9–26.6% and 26.2–65.6%/1.6–47.5% of readings among the mixed and hypertensive sub-populations respectively.

The proportion of clinically significant differences between readings including FBPR and those excluding FBPR reduced greatly in the average measurement models. For each

TABLE 1. BLOOD PRESSURE VARIABLES INVOLVED IN THE COMPARATIVE ANALYSES

Variables	*Final study population* n = *170 (mmHg)*	*Hypertensive sub-population* n = *61 (mmHg)*	*Mixed sub-population* n = *109 (mmHg)*
SYS-1	93–244 (146 ± 32.4)	112–244 (164.9 ± 32.2)	93–228 (135.5 ± 27.4)
DIA-1	44–143 (86.3 ± 17.3)	44–143 (95.4 ± 15.4)	55–136 (81.2 ± 16.2)
SYS-2	87–250 (141.8 ± 31.1)	105–250 (159.7 ± 31.8)	87–225 (131.8 ± 25.8)
DIA-2	51–143 (83.9 ± 16.4)	60–143 (92.6 ± 14.3)	51–129 (79.1 ± 15.5)
SYS_{1-3}	90–248 (141.9 ± 31.1)	109–249 (160.3 ± 31.4)	90–223 (131.6 ± 25.9)
DIA_{1-3}	52–143 (84.1 ± 16.6)	59–143 (93.1 ± 14.5)	52–130 (79.1 ± 15.7)
SYS_{2-4}	88–250 (138.4 ± 30.4)	100–250 (156 ± 31.2)	88–220 (128.6 ± 25.2)
DIA_{2-4}	49–143 (82.3 ± 16.3)	54–143 (90.6 ± 14.3)	49–128 (77.7±15.6)
SYS_{1-5}	89–249 (139.1 ± 30.4)	103–249 (156.9 ± 30.9)	89–219 (129.2 ± 25.2)
DIA_{1-5}	49–143 (82.5 ± 16.3)	55–143 (91.1 ± 14.3)	50–128 (77.7 ± 15.4)
SYS_{2-6}	87–250 (136.5 ± 29.8)	103–250 (153.9 ± 30.6)	87–220 (126.8 ± 24.5)
DIA_{2-6}	49–142 (81.5 ± 16.6)	53–142 (90.1 ± 14.7)	49–126 (76.6 ± 15.7)

TABLE 2. DIFFERENCES BETWEEN COMPARED READINGS

Differences	*Range (mean ± SD*) (mmHg)*	*0 mmHg* n *(%)*	*< 5 mmHg* n *(%)*	*≥ 5 mmHg* n *(%)*
Mixed sub-population				
SYS-1 – SYS-2	0–31 (6.9 ± 5.9)	9 (8.3)	47 (43.1)	62 (56.9)
SYS_{1-3} – SYS_{2-4}	0–11 (3.4 ± 2.7)	14 (12.8)	77 (70.6)	32 (29.4)
SYS_{1-5} – SYS_{2-6}	0-11 (2.5 ± 2.0)	14 (12.8)	89 (81.7)	20 (18.3)
DIA-1 – DIA-2	0–16 (3.8 ± 3.1)	6 (5.5)	80 (73.4)	29 (26.6)
DIA_{1-3} – DIA_{2-4}	0–6 (1.6 ± 1.4)	25 (22.9)	105 (96.3)	4 (3.7)
DIA_{1-5} – DIA_{2-6}	0–21 (1.6 ± 2.1)	15 (13.8)	108 (99.1)	1 (0.9)
Hypertensive sub-population				
SYS-1 – SYS-2	0–30 (9 ± 7.5)	4 (6.6)	21 (34.4)	40 (65.6)
SYS_{1-3} – SYS_{2-4}	0–20 (5 ± 3.8)	2 (3.3)	31 (50.8)	30 (49.2)
SYS_{1-5} – SYS_{2-6}	0–11 (3.3 ± 2.5)	8 (13.1)	45 (73.8)	16 (26.2)
DIA-1 – DIA-2	0–24 (5.1 ± 4.5)	4 (6.6)	32 (52.5)	29 (47.5)
DIA_{1-3} – DIA_{2-4}	0–34 (3 ± 4.4)	7 (11.5)	54 (88.5)	7 (11.5)
DIA_{1-5} – DIA_{2-6}	0–19 (1.9 ± 3.4)	5 (8.2)	60 (98.4)	1 (1.6)

measurement model, the hypertensive sub-population had higher proportions of clinically significant differences (≥ 5 mmHg) between the compared readings than the mixed sub-population. However, the differences between the sub-populations in the proportion of differences (≥ 5 mmHg) were not statistically significant.

Systolic and diastolic readings that included FBPR had strong statistically significant correlations to those excluding FBPR [Pearson's correlation coefficient (r) 0.86–1.00, $p < 0.0001$ for all pairs of comparisons]. Scatter plots depicting these strong correlations as well as their coefficients (and 95% confidence intervals for the correlation coefficients) are shown in Figs 1 and 2 for systolic and diastolic readings, respectively.

The distributions of the subjects' BP in the JNC-7 model (mixed sub-population) and a modified JNC-7 model (hypertensive sub-population) are shown in Table 3. No statistically significant difference was found in the pattern of distribution between the readings in all the comparisons within each sub-group.

Table 4 shows the changes in the distribution of subjects' BP relative to a threshold value of 140/90 mmHg. It was observed that in the final study population, hypertensive sub-population and mixed sub-population, respectively, non-statistically significant differences were obtained in the distribution of BP values into < 140/90 mmHg and ≥ 140/90 mmHg groups by readings inclusive or exclusive of FBPR ($p > 0.05$ for all, Fisher's exact tests).

Discussion

In this study, comparative analysis was used to evaluate the effect of the first office BP reading on hypertension-related clinical decisions using single, triple and quintuple measurement models. Our results showed that mean readings that included or excluded FBPR (systolic and diastolic, respectively) within the final study population and the sub-populations did not differ in statistical significance.

The distribution of blood pressure readings for the hypertensive and mixed sub-populations in the classes defined by the JNC-7 model or its modification did not reveal any statistically significant difference relating to inclusion or exclusion of the FBPR for single, triple or quintuple measurements. Similarly, the distribution of the analysed blood pressure readings relative to a threshold of 140/90 mmHg did not differ significantly between readings that included or excluded FBPR.

A non-statistically significant difference was found between the hypertensive and mixed sub-populations in the comparison of the proportions of differences between readings that included and excluded the FBPR, which were: clinically significant (≥ 5 mmHg); and 0 mmHg. Lastly, we found that readings that included the FBPR were strongly correlated to those excluding the FBPR.

Overall, our findings suggest that: (1) for patient populations with known hypertensive status, the use of FBPR as a single reading or its inclusion in repeated readings for deriving average BP values may not have a significant effect on clinical decisions

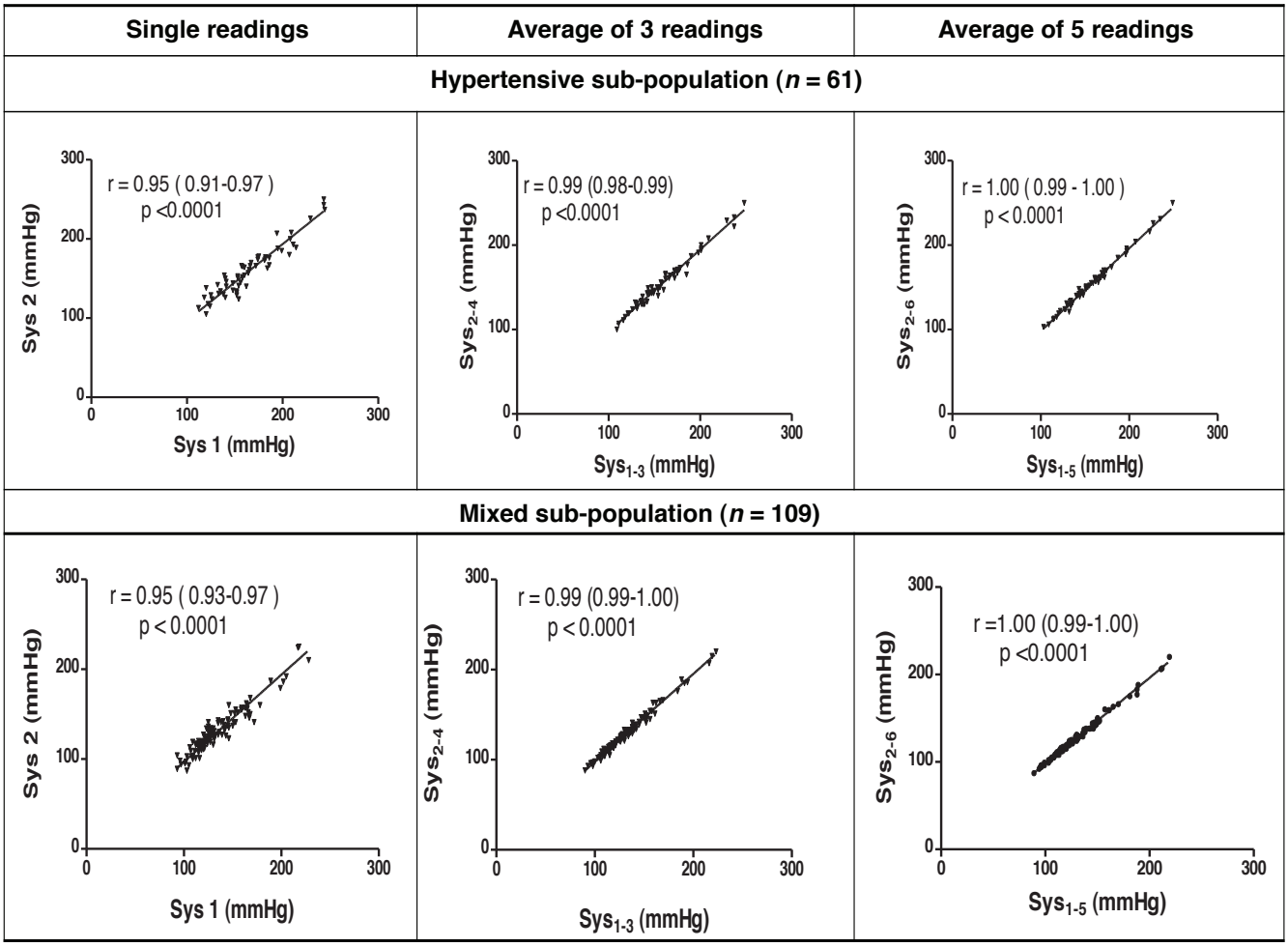

Fig. 1. Correlation scatter plots and coefficients for compared systolic readings.

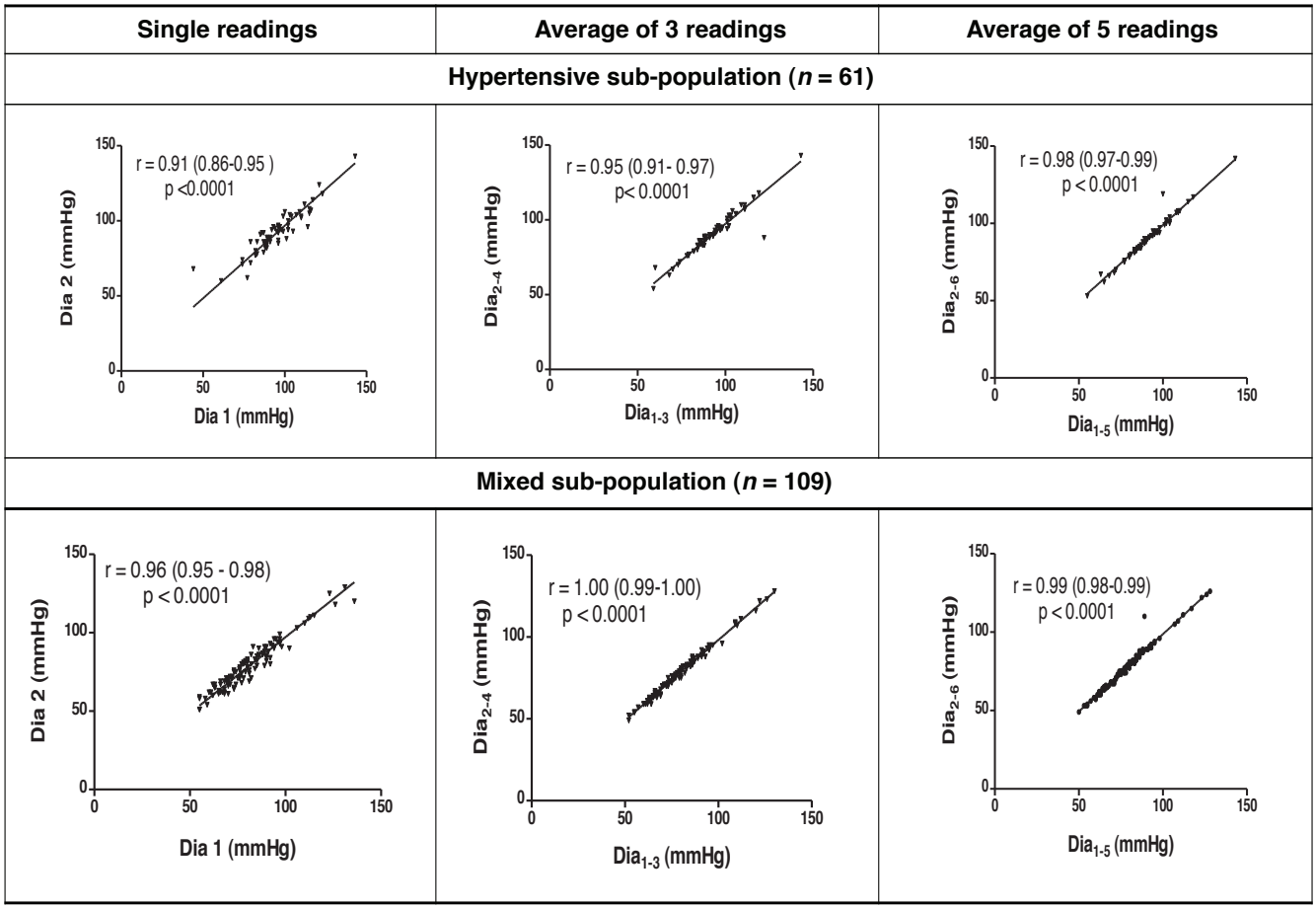

Fig. 2. Correlation scatter plots and coefficients for compared diastolic readings.

regarding BP control or staging of current hypertensive status for uncontrolled individuals; (2) for patient sub-populations with undetermined hypertensive status (commonly encountered in

TABLE 3. DISTRIBUTION OF BLOOD PRESSURE READINGS FROM COMPARED VARIABLES USING CLASSICAL AND MODIFIED JNC-7 MODELS

Variables	*Optimal*	*Pre-HTN*	*Stage I*	*Stage II*	*ISH*	χ^2 *(4 df)*	p-*value*
Mixed sub-population (*n* = 109)							
FBPR	37	30	14	14	14	1.37	0.84
SBPR	43	28	11	16	11		
AVE_{1-3}	41	34	12	10	12	2.10	0.72
AVE_{2-4}	45	37	6	10	11		
AVE_{1-5}	43	37	9	9	11	0.45	0.93
AVE_{2-6}	48	35	7	10	9		
Variables	*Stage 0*		*Stage I*	*Stage II*	*ISH*	χ^2 *(3 df)*	p-*value*
Hypertensive sub-population (modified JNC-7 model) (*n* = 61)							
FBPR	11		9	30	11	0.37	0.95
SBPR	13		9	27	12		
AVE_{1-3}	13		11	25	12	1.02	0.80
AVE_{2-4}	16		8	23	14		
AVE_{1-5}	17		11	21	12	0.46	0.93
AVE_{2-6}	16		11	19	15		

Pre-HTN = pre-hypertension; ISH = isolated systolic hypertension, χ^2 (4 df) = Chi-square test with 4 degrees of freedom, χ^2 (3 df) = Chi-square test with 3 degrees of freedom.

TABLE 4. COMPARISON OF THE DISTRIBUTION OF BLOOD PRESSURE READINGS RELATIVE TO A THRESHOLD VALUE OF 140/90 mmHg

Variables	*<140/90 mmHg*	*≥ 140/90 mmHg*	p-*value**
Final study population (*n* = 170)			
FBPR	79	91	
SBPR	86	84	0.52
AVE_{1-3}	88	82	
AVE_{2-4}	97	73	0.38
AVE_{1-5}	96	74	
AVE_{2-6}	100	70	0.74
Mixed sub-population (*n* = 109)			
FBPR	67	42	
SBPR	71	38	0.67
AVE_{1-3}	75	34	
AVE_{2-4}	82	27	0.37
AVE_{1-5}	80	29	0.76
AVE_{2-6}	83	26	
	Controlled	*Uncontrolled*	
Hypertensive sub-population (*n* = 61)			
FBPR	11	50	0.82
SBPR	13	48	
AVE_{1-3}	13	48	0.67
AVE_{2-4}	16	45	
AVE_{1-5}	17	44	1.00
AVE_{2-6}	16	45	

*Fisher's exact test.

general outpatient clinics), the use of FBPR as a single reading or its inclusion in repeated readings for deriving average BP values may not have a significant effect on clinical decisions regarding BP classification or consideration for a diagnosis of hypertension; (3) in terms of clinically significant absolute differences (≥ 5 mmHg) between readings including and excluding FBPR, differences between a purely hypertensive population and a mixed population may not be of statistical significance. This suggests that a recommendation for the exclusion of FBPR for either of the population groups may not be clinically useful.

We observed that the issue of whether or not to discard the FBPR is an important one that has not received adequate research attention. Considering the fact that blood pressure measurement is associated with transient discomfort to the patient, subjecting patients to uncomfortable (albeit transient) cuff inflation and deflation to obtain a reading that will be discarded without a scientifically sound reason is unjustifiable. Discarding the FBPR is associated with the expending of patient and personnel time as well as energy. The consequence of this will be particularly relevant in resource-poor settings.

Graves and Grossardt had earlier found that discarding the first of three nurse-auscultatory or oscillometric blood pressure measurements did not improve the association of office blood pressure with ambulatory blood pressure readings.[11] Despite conducting an extensive literature review, we were unable to identify any previous study that addressed this issue with sets of readings from the same BP monitor. However, it is noteworthy to state that Mengden *et al*. were the first to report that patients are also inclined to discard the first reading in home monitoring of blood pressure.[12] It is not unlikely that this practice may have been acquired by the patients from physicians or nurses.

In our study, we focused on a single oscillometric device, the BpTRU, because it was designed for automated exclusion of the first BP reading. The value of this BpTRU design in improving the association between OBP and ABPM has been reported by Beckett and Godwin.[13] Their findings suggested that by discarding the first reading, the improvement resulted from a reduction in the white-coat effect. Therefore, while this device may reduce the white-coat effect in comparative studies that involved other devices with different principles and algorithms, in our study, it has clearly been unable to justify the effect of discarding the first reading on important parameters that often guide hypertension-related clinical decisions.

We avoided the use of more than one device or additional auscultatory measurements because of confounding factors that could be introduced. Furthermore, it was considered that six BP readings at one sitting were taxing enough for our participants.

Important limitations of our study include the relatively small sample size. However, evaluation of our objectives in sub-populations showed that findings within the final study population were not likely due to chance. Also, these findings may not necessarily apply to automated oscillometric measurements in the home setting.

The strengths of this study lie in the wide range of blood pressure values that were involved and the use of a general out-patient population, which enabled us to perform sub-group analyses of hypertensive and undifferentiated sub-populations. There is a need for further studies with larger sample sizes to create more robust evidence on this important clinical subject. Also, investigation of the inclusion or exclusion of the first blood pressure reading in HBPM will illuminate its effect on the diagnosis and control of hypertension with the use of HBPM readings.

Conclusion

Our findings suggest that exclusion of the first office BP reading is not likely to have a significant impact on hypertension-related clinical decisions.

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Review Article

The effects of medicinal plants on renal function and blood pressure in diabetes mellitus

CT MUSABAYANE

Abstract

Diabetes mellitus is one of the most common chronic global diseases affecting children and adolescents in both the developed and developing nations. The major types of diabetes mellitus are type 1 and type 2, the former arising from inadequate production of insulin due to pancreatic β-cell dysfunction, and the latter from reduced sensitivity to insulin in the target tissues and/or inadequate insulin secretion. Sustained hyperglycaemia is a common result of uncontrolled diabetes and, over time, can damage the heart, eyes, kidneys and nerves, mainly through deteriorating blood vessels supplying the organs. Microvascular (retinopathy and nephropathy) and macrovascular (atherosclerotic) disorders are the leading causes of morbidity and mortality in diabetic patients. Therefore, emphasis on diabetes care and management is on optimal blood glucose control to avert these adverse outcomes.

Studies have demonstrated that diabetic nephropathy is associated with increased cardiovascular mortality. In general, about one in three patients with diabetes develops end-stage renal disease (ESRD) which proceeds to diabetic nephropathy (DN), the principal cause of significant morbidity and mortality in diabetes. Hypertension, a well-established major risk factor for cardiovascular disease contributes to ESRD in diabetes. Clinical evidence suggests that there is no effective treatment for diabetic nephropathy and prevention of the progression of diabetic nephropathy. However, biomedical evidence indicates that some plant extracts have beneficial effects on certain processes associated with reduced renal function in diabetes mellitus. On the other hand, other plant extracts may be hazardous in diabetes, as reports indicate impairment of renal function. This article outlines therapeutic and pharmacological evidence supporting the potential of some medicinal plants to control or compensate for diabetes-associated complications, with particular emphasis on kidney function and hypertension.

Keywords: diabetes mellitus, diabetic nephropathy, medicinal plants, hypertension

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Diabetes mellitus is a global disease affecting both the developed and developing nations. Epidemiological data suggest that at least one in 20 deaths are attributable to diabetes and related complications, a proportion which increases to at least one in 10 deaths in adults aged 35 to 64 years.[1] The figure is considered to be an underestimate since most individuals die from cardiovascular and renal-related complications.[2] World Health Organisation data show that the age-standardised death rate for diabetics in South Africa is 85 per 100 000. Death rates in other sub-Saharan African countries range from 21 to 49 per 100 000, compared with 18 in the USA and six per 100 000 in the UK.[3]

The principal causes of mortality in type 1 and 2 diabetes patients are disorders grouped as microvascular (retinopathy and nephropathy) and macrovascular (atherosclerotic) complications.[4,5] Macrovascular diseases account for the majority of deaths in type 2 diabetes patients, and the presence of hypertension is associated with a four- to five-fold increase in mortality.[6] A causal relationship between chronic hyperglycaemia and diabetic microvascular disease, long inferred from various animal and clinical studies,[7] has now been established by data from the Diabetes Control and Complications Trial (DCCT) controlled clinical study.[8]

Conventional diabetes therapy using blood glucose-lowering agents such as sulphonylureas, insulin therapy, α-glucosidase inhibitors, peroxisome proliferator gamma (PPAR-γ) agonists and biguanides has limitations. For instance, insulin therapy does not achieve glycaemic control in patients with insulin resistance, and oral hypoglycaemic agents may lose their efficacy after prolonged use. Previous studies elsewhere suggest that insulin is not only ineffective in preventing type 1 diabetes in patients at risk of developing this condition, but it can also cause cardiovascular disease.[9,10] Furthermore, conventional drugs are not easily accessible to the general population in developing countries due to socio-economic conditions.[11,12] Hence there is an urgent need to find affordable treatments that are effective in slowing the progression of diabetic complications.

Traditional herbal medicine is used by many rural African communities to treat a range of diseases, including diabetes. Anecdotal evidence suggests that diabetic complications are less common in rural populations, attributable to either the beneficial effect of plant medicines or to the fact that other risk factors that aggravate diabetes in the urban context are less prevalent in rural situations. The World Health Organisation not only encourages the use of plant medicines, but also recommended scientific evaluation of the hypoglycaemic properties of plant extracts.[13] Estimates indicate that more than 70% of the world's

population uses resources derived from traditional medicine to control diabetes.[14] Medicinal-plant home remedies are used as crude extracts or standard, enriched fractions in pharmaceutical preparations.

Research summarised in a recent review[15] showed that several southern African plant species used by rural communities as traditional medicines had hypoglycaemic effects in streptozotocin-induced (STZ) diabetic rat. Furthermore, some species had antihypertensive properties.[16-19] The impact on the kidney varies, with some species being reno-protective, whereas others had a deleterious effect on kidney function. By identifying the bio-active compound, oleanolic acid (OA), which confers reno-protection, we have been able to demonstrate the effectiveness of this agent in STZ diabetic rats.

The focus of this article is to evaluate current evidence on plant extracts used for the management of hypertension and kidney disease in diabetes. The beneficial as well as deleterious effects of medicinal plants in both conditions are discussed based on reports on plants frequently used in the southern Africa setting. Herein, a medicinal plant is defined as any plant which provides health-promoting characteristics, temporary relief or has curative properties.

Antihypertensive therapy and diabetic renal disease

Diabetic complications, which include damage to large and small blood vessels, can lead to coronary heart disease, stroke and hypertension, the latter being a well-established major risk factor for cardiovascular disease that contributes to end-stage renal disease (ESRD). Reduction of blood pressure (BP) is therefore an efficient way of preventing or slowing the progression of ESRD. Conventionally, reno-protection is achieved through reduction in BP with antihypertensive regimens.[20-23] Several studies however document that antihypertensive treatment in diabetes not only improves the quality of life,[24-27] but also reduces renal complications.[28]

The major antihypertensive drug classes widely used include thiazide diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), β-blockers, central sympatholytic agents, calcium channel antagonists and other vasodilators. However, some antihypertensive agents, for example, thiazide diuretics and β-blockers deleteriously influence glycaemic control.[29]

To date, the most effective treatments for diabetic nephropathy (DN) are the antihypertensive drugs, particularly those that target the renin–angiotensin system (RAS) such as ACE inhibitors, angiotensin-1 receptor antagonists, or their combination.[25,30,31] Although these treatments may retard the progressive decline in renal function in diabetes, clinical trials suggest that there is no effective treatment for DN.[8]

For these reasons, novel anti-diabetic therapeutic agents that supplement, substitute or complement the existing modern medications to ameliorate renal function in diabetes constitute novel therapeutic strategies for diabetes. Evidence from biomedical literature suggests that some plant extracts have protective effects against cardiovascular disease in diabetes.[32] The following sections evaluate the therapeutic and pharmacological evidence for the use of some of the medicinal plants and their bioactive phytochemicals in cardio-renal related diabetic complications, as well as the potential for nephrotoxicity from other plant extracts.

Natural plants for cardiovascular disease

Several plant extracts with potential therapeutic properties for the treatment of hypertension and complications such as coronary heart disease, angina, arrhythmias and congestive heart failure have been identified.[33-36] Traditional medicinal healers in southern Africa have used *Helichrysum ceres* S Moore [Asteraceae] to treat kidney and cardio-respiratory disorders.[37] Recent laboratory studies suggest that the hypotensive effects of *H ceres* leaf extract in anaesthetised male Sprague-Dawley rats could in part be attributed to the extract's natriuretic and diuretic properties.[38] We reported that *H ceres* ethanolic leaf extract's hypotensive effects were elicited in part by the direct relaxant effects on cardiac and vascular smooth muscles.[39] The data suggested that lowering of blood pressure was due to reduced peripheral resistance elicited by the extract's vasodilatatory effects on the vascular smooth muscles, mediated in part via the endothelium-derived factors (EDRF). This suggestion was corroborated by the observations that *H ceres* leaf extract elicited potent negative inotropic and chronotropic effects *in vivo* and exhibited vasorelaxant effects in vascular tissue preparations.

We also reported that *Ekebergia capensis* Sparrm (Meliaceae) leaf extract prevented the development of hypertension in weanling genetically hypertensive Dahl salt-sensitive (DSS) rats, which develop hypertension as they age.[19] The *in vivo* reduction in blood pressure by the extract occurred without significant alterations in the heart rate, suggesting that the *in vitro* cardiovascular effects of the extract significantly contributed to the hypotensive effects. Indeed, studies showed that the hypotensive effect of *E capensis* leaf extract was in part mediated via modulation of total peripheral resistance of the vascular smooth muscles, as evidenced by the extract's elicited dose-dependent vasorelaxations in endothelium-intact and endothelium-denuded aortic ring preparations. It should be noted that lanoxin, one of the cardiac glycosides found in a number of plants, has specific effects on the myocardium.

Kidney function changes in diabetes mellitus

Sustained hyperglycaemia is the main cause of the changes in kidney function in diabetes mellitus. Hyperglycaemia leads to the increased formation of advanced glycation end-products (AGEs), oxidative stress, activation of the polyol pathway and hexosamine flux, causing inflammation and renal damage.[40] AGEs result in the increased production of extracellular matrix proteins in endothelial cells, mesangial cells and macrophages in the kidney.[41] Additionally, AGEs have been shown to reduce matrix protein flexibility through cross-link formation of the extracellular matrix proteins, leading to an abnormal interaction with other matrix components.[41]

Irrespective of all the other structural and functional changes, the mesangial alterations appear to be the main cause of declining renal function in experimental diabetic animal models.[42] For example, hyperfiltration, which occurs in the early stages of DN has been attributed to increased mesangial production of vascular permeability factors in response to stretching.[43] The subsequent decline in glomerular filtration rate (GFR) as nephropathy progresses may be due to expansion of the mesangial matrix,

which compresses the glomerular capillaries, thereby reducing the filtration surface area and impairing the mechanism that maintains the normal glomerular capillary hydrostatic pressure.[42] The fall in GFR also reduces the sodium load delivered to the macula densa cells, resulting in enhanced tubulo-glomerular feedback (TGF).[44] In turn angiotensin II production increases due to hyperactivation of the renin–angiotensin–aldosterone system,[45] causing more reabsorption of sodium and an increase in systemic blood pressure.

The accumulation of AGEs can be prevented by antioxidants such as flavonoids or by preventing the glucose-dependent formation of intermediate products (Amadori, Schiff bases or Milliard products). Indeed, blocking or deleting AGEs' receptor (RAGE) in experimental animals reversed atherosclerosis.[46] Amino guanidine and pyridoxamine, AGEs formation inhibitors, had reno-protective effects in diabetic animals.[47,48] Furthermore, inhibition of AGEs effects could be achieved through breaking of the AGEs cross links by drugs such as alagebrium or inhibition of AGE signal transduction.[48]

Tanaka *et al*.[49] reported that the biguanide metformin, the only example of an approved antidiabetic from a herbal source, French lilac (*Galega officinalis*) may be useful in the prevention of the development of AGEs. The *Panax quinquefolium* (Linnaeus) [Araliaceae] extracts, a phyto-oestrogen derived from *Vitis vinifera* (Linnaeus) [Vitaceae] (resveratrol), curcumin from *Curcuma longa* (Linnaeus) [Zingiberaceae] and glycosides from *Stelechocarpus cauliflorus* (RE Fr) [Annonaceae] have also been reported to inhibit formation of AGEs or RAGE.[50-56]

Diabetic nephropathy

Renal disease is a common and often severe complication of diabetes, with the majority of patients with 18 years' duration showing signs of diabetic renal involvement.[57] In general, about one in three patients with type 1 or 2 diabetes develops ESRD which proceeds to DN, the principal cause of significant morbidity and mortality in diabetes.[8] The onset of DN is associated with a progressive rate of decline in renal function, urinary albumin excretion and glomerular filtration rate. For purposes of this discussion, DN is used as a generic term referring to any deleterious effect on kidney structure and/or function caused by diabetes mellitus.

Management of diabetic nephropathy

World Health Organisation data report age-standardised death rate for diabetics in South Africa is 85 per 100 000 compared with 18 in the USA and six per 100 000 in the UK.[3] The principal reason for the high mortality rates in South Africa is renal failure as a result of DN. Some 30 to 40% of diabetics develop nephropathy, which is the leading cause of ESRD.[14]

DN progresses through five well-defined stages.[58] Stage 1 is an increase in GFR, which progresses to the clinically silent stage 2, in which hyperfiltration is associated with hypertrophy. Stage 3, or initial nephropathy, is typified by microalbuminuria, modest increases in blood pressure and a reduction in GFR. Stage 4 sees macroalbuminuria, raised blood pressure and progressive reductions in GFR, leading to stage 5 or ESRD when renal-replacement therapy is required.

ESRD is managed in developed countries by renal replacement therapy (RRT), such as dialysis and transplantation. In developing countries, however, kidney failure rates are double those in the West because access to RRT is severely limited by its high cost to patients.[13] The figures are stark: 70% of patients in a Nigerian study were able to afford dialysis for only one month, with less than 2% having sufficient resources to remain on dialysis for more than 12 months.[59] Access to RRT is virtually impossible for the rural poor.[12]

Current conventional diabetes therapy using blood glucose-lowering medications has limitations in averting renal complications. Progression towards ESRD may be slowed in part by strict control of blood sugar levels and blood pressure, a reduction in dietary protein intake and inhibition of the renin–angiotensin system. Consequently, drug developmental strategy should target these metabolic pathways for the prevention of progression to ESRD, which proceeds to DN.

Many patients of sub-Saharan Africa however cannot afford these expensive drugs. Hence there is an urgent need to find affordable treatments which are effective in slowing the progression of DN.

Medicinal plants in the management of diabetic kidney disease

Ethno-medicinal plants have traditionally been used for the treatment of diabetes and its complications. In fact, current pre-clinical and clinical studies have demonstrated that many have beneficial effects on some processes associated with reduced renal function in experimental animals.[60-62] The active phytochemicals responsible for their activities have also been identified.

Our research has established the therapeutic and pharmacological properties of a number of ethno-botanical herbs traditionally used in the management of diabetes mellitus by African communities.[15] Observations indicate that some herbal extracts contain compounds that could be effective in mild diabetes mellitus or in cases of impaired glucose tolerance (Fig. 1). These are likely to have a positive impact on glucose homeostasis in diabetic patients.

Investigations from our laboratory have also examined whether herbal extracts could lower blood pressure or improve

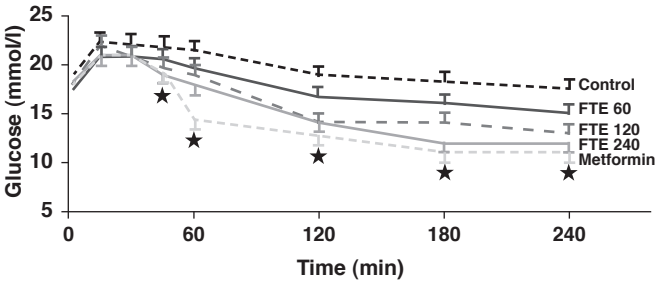

Fig. 1. Oral glucose tolerance test in STZ-diabetic rats showing dose-related reduction in plasma glucose levels following treatment with *F thonningii* bark ethanolic extracts (FTE, 60–240 mg/kg) comparable to that induced by metformin (500 mg/kg).[17] Statistical comparison of the differences between the control and experimental group means was performed using one-way analysis of variance (ANOVA) followed by Tukey-Kramer multiple comparison test. A value of $p < 0.05$ was considered significant.

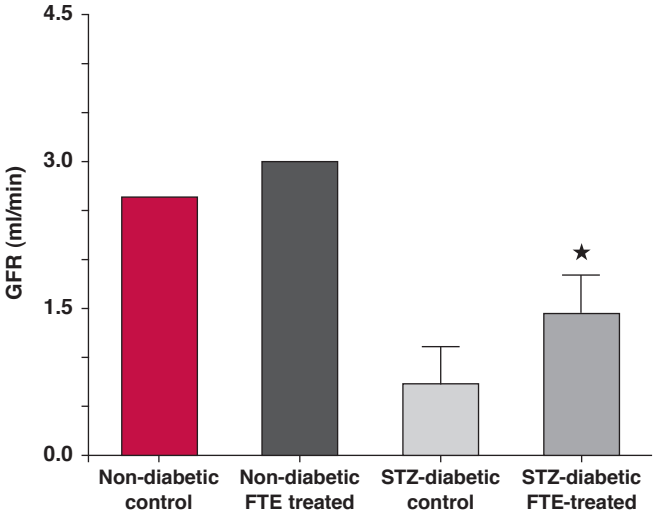

Fig. 2. Sub-chronic treatment with *F thonningii* bark ethanolic extracts (FTE) every third day increased glomerular filtration rate in STZ-diabetic rats.[63]

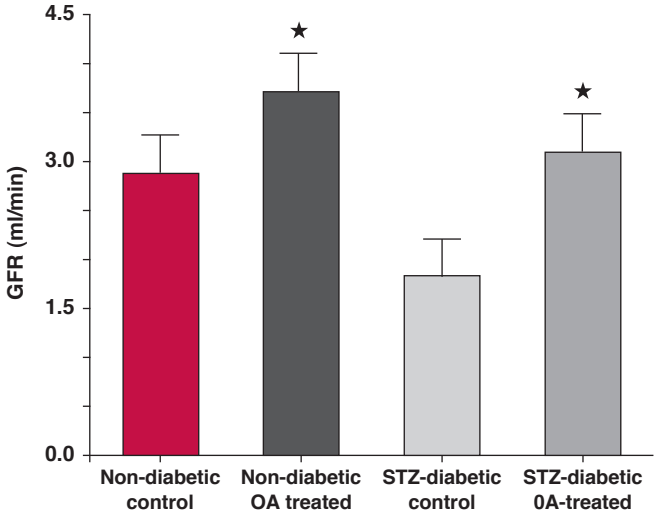

Fig. 3. Sub-chronic treatment with oleanolic acid (OA, 60 mg/kg bid every third day) increased glomerular filtration rate in STZ-diabetic rats.[66]

the impaired renal and cardiovascular functions often seen in diabetes. The results suggest that while some extracts such as *Hypoxis hemerocallidea* corm aqueous extract (APE) had hypoglycaemic effects, they may have deleterious effects on kidney function. Gondwe *et al*. found that APE increased renal fluid output and electrolyte retention, and reduced glomerular filtration rate,[32] neither of which are desirable in diabetes mellitus. In contrast, other studies from our laboratories have shown that

TABLE 1. PARTIAL SURVEY OF MEDICINAL PLANTS/PLANT EXTRACTS WHICH AFFECTED THE CARDIOVASCULAR AND KIDNEY FUNCTION IN DIABETES MELLITUS.

Botanical species	*Bioactive compounds*	*Antidiabetic advantages*	*Renal function advantages*	*Cardiovascular advantages*	*References*
Allium sativum L (garlic) (Alliaceae)	phenols flavonoids	↑ insulin secretion ↑ hepatic glycogen	↑ GFR	vasorelaxant, ↓ hypolipidaemic	67, 68
Gongronema latifolium	flavonoids saponins polyphenols	↑ hepatic glycogen	anti-oxidant	↓ hypolipidaemic	69
Foeniculum vulgare L (Apiaceae)	phytoestrogens	↓ glucose absorption	diuretic natriuretic	vasorelaxant	70
Opuntia megacantha	phenols, flavonoids (quercetin) taxifolin	↓ glucose absorption	↑ GFR	vasorelaxant	71, 72, 73
Syzygium spp	phenylpropanoids flavonoids sesquiterpenes oleanolic acid rhamnetin	↑ hepatic glycogen ↑ insulin secretion	↑ GFR anti-oxidant	vasorelaxant	63, 66, 74
Sclerocarya birrea [(A Rich) Hochst] [Anacardiaceae]	flavonoids, alkaloids, triterpenoids, coumarins, ascorbic acid	↑ hepatic glucose utilisation ↑ insulin secretion	↑ GFR	vasorelaxant	32, 75
Persea americana Mill (Lauraceae) [Avocado]	tannins, saponins flavonoids, alkaloids glycosides	↑ hepatic glycogen ↑ insulin secretion	↑ GFR	vasorelaxant bradycardia ↓ hypolipidaemic	32, 76, 77, 78
Hypoxis hemerocallidea	glycoside hypoxoside β-sitosterol sterolins, cytokinins	↑ insulin secretion	reno-toxic ↓ GFR	cardiodepressant bradycardia	79, 80
Ficus thonningii (Blume) [Morarceae]	alkaloids anthraquinones flavonoids saponins tannins	↑ hepatic glycogen	↑ GFR	cardiodepressant vasorelaxant bradycardia	17, 81
Olea europaea L, (Oleaceae)	triterpenes, flavonoids, glycosides	↑ insulin secretion ↑ glucose utilisation	↑ GFR antioxidant	cardiodepressant vasorelaxant bradycardia	36, 82, 83, 84
Helichrysum ceres S Moore [Asteraceae]	polyphenols, tannins, triterpenes saponins	unclear	diuretic natriuretic	cardiodepressant vasorelaxant, bradycardia	38, 39
Ekebergia capensis Sparrm (Meliaceae)	saponins alkaloids flavonoids tannins	unclear	unclear	cardiodepressant vasorelaxant bradycardia	85

Opuntia megacantha leaf extract, which had hypoglycaemic effects, reversed the inability of the kidney to excrete Na^+ in STZ diabetes mellitus, suggesting that this plant may be beneficial.[17]

We undertook a systematic survey of medicinal plants used by rural communities in South Africa and have identified several species with beneficial effects in the prevention of renal complications in diabetes mellitus. These effects were observed with both crude extracts and bioactive compounds isolated from antidiabetic plants. In particular, we showed that plants such as *Sclerocarya birrea* [(A Rich) Hochst] [Anachardiaceae], *Persea americana* (Miller) [Lauraceae], *Ficus thonningii* (Blume) [Moraceae] and *Helichrysium ceres* had reno-protective effects (Fig. 2).[17,32,38] Initial studies have shown that extracts from these plants ameliorated renal dysfunction in experimental diabetes.

Subsequently, we isolated oleanolic acid as the bioactive compound and have shown that it possesses reno-protective effects in experimental diabetes mellitus. Therefore *S cordatum*-derived oleanolic acid caused increased renal Na^+ excretion in STZ-induced diabetic rats, which was mediated by an improvement in glomerular filtration rate (Fig. 3).[63] Other active agents identified in these plants include polysaccharides, flavonoids, xanthones and peptides.

There are various mechanisms by which reno-protection may be achieved, including modulation of AGEs, of the polyol pathway, and of the PKC pathway, and anti-oxidative properties. For example, morroniside isolated from *Corni fructus* has shown reno-protection in experimental diabetes through a reduction in the production of AGEs.[64] Additionally, some plants have been shown to cause an improvement in renal function in experimental diabetes mellitus through inhibition of ET-1 and TGF-β_1 and the endothelin-1 receptor A (ETRA).[65]

Available evidence suggests that some herbal extracts interfere with the concentrating and diluting mechanisms of tubular transport processes in the proximal and distal tubules and/or on other components of tubular cell membranes. Therefore we speculate that oleanolic acid influences renal fluid and electrolyte handling by altering the structural integrity and function of tubular epithelial cells to affect reabsorption and secretion.

Modification of risk factors in diabetes has an impressive impact on morbidity and mortality in diabetic patients. An overview of some of some medicinal plants currently used in diabetic hypertension and kidney disease, together with the possible mechanism(s) is summarised in Table 1.

Conclusion

We describe the therapeutic and pharmacological evidence in support of some of the medicinal plant extracts used in the management of hypertension and kidney disease in diabetes mellitus. Some of these medicinal plant extracts are a potential source of anti-diabetic drugs because of their therapeutic efficacy and anti-diabetic mechanisms reported in experimental animals. However, at present, the cellular/molecular mechanisms of action of these plant extracts remain to be established.

Future research directed at the identification of active components is the only viable option for supporting the efficacy claims for all herbs. In the absence of such standardisation, health practitioners and consumers alike should remain optimistic but wary. Research funding to investigate potentially beneficial effects of medicinal plants is critically important for optimal patient care and safety.

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Letter to the Editor

A systematic overview of prospective cohort studies of cardiovascular disease in sub-Saharan Africa: reply to Bovet *et al*., and Gao *et al*.

Dear Sir

Two groups of investigators have recently provided evidence supporting the need for elaborated longitudinal studies to inform successful health service and policy solutions to the growing problem of chronic and cardiovascular disease in sub-Saharan Africa (SSA).[1-3] In one of those studies, published in the *Cardiovascular Journal of Africa*,[1] our group reached such a conclusion on the basis of a systematic review of relevant existing cohort studies conducted in SSA, published and indexed to MEDLINE from 1966 to October 2009.[1]

The feedback received from colleagues both from Africa and beyond testifies to the interest and also the expectations of the scientific community at large for longitudinal studies on chronic diseases in SSA. We are particularly grateful to Drs Bovet and Shamlaye,[4] and Drs Gao and Yuan,[5] who through two letters published in the *Cardiovascular Journal of Africa*, have made a significant contribution to the debate.

Drs Bovet and Shamlaye[4] provided evidence suggesting that our review missed some relevant studies fulfilling our entry criteria and published in leading medical journals. They further suggested that we omitted some SSA countries from our search. We did acknowledge in the limitations sections of our article that for a number of reasons, there was still a possibility that our search did not capture all relevant studies. Therefore, we welcome the contribution of Bovet and Shamlaye and call for an ongoing register of African cohort studies, possibly in the columns of the *Cardiovascular Journal of Africa* along the lines of the cohort profiles in the *International Journal of Epidemiology*.[6]

However, of the eight studies listed by the two colleagues, at least four do not fulfil the eligibility criteria of our review, including a study from Mauritius published one year after the completion of our review,[7] a study with a follow-up duration shorter than six months,[8] one in which none of the predictors of interest was assessed at baseline,[9] and one cross-sectional study with no follow-up component.[10] It would have been more appropriate to repeat the systematic search using our strategy, or any other judged appropriate by the authors, and quantify the gap, if any, between our study and what should have been optimal.

Furthermore, unlike the authors' suggestion, we made no restriction by country or importance of the journal of publication in our search, nor did we claim that cohort studies have not been conducted in Africa. Notwithstanding the above shortcomings, the many similarities between the studies presented by the authors and those included in our review in terms of limitations of the data available further strengthen our conclusions. Some of those limitations include the small sample size, the short duration of follow up and the high rate of drop-out during follow up.

Drs Gao and Yuan also suggested that our work did not cover all aspects of the relationship between cardiovascular disease and related risk factors.[5] Their claim is absolutely right and would apply to even the landmark Framingham study,[11,12] which over the course of more than 60 years, has not yet covered all aspects of the interaction between determinants and cardiovascular diseases. The broadness of the cardiovascular disease field definitely invited some prioritisation in the course of our study. This prioritisation was based on the knowledge from the literature of important cardiovascular diseases and their major determinants, those cardiovascular diseases and risk factors which are likely more important in the African setting.

From our experience researching cardiovascular diseases in Africa, we had several strong indicators that existing relevant cohort studies, if any, would singly not be sufficient to address major gaps in knowledge. Therefore our aim, as stated in our article, was to identify existing cohort studies and assess whether these could be combined to increase the statistical power for answering major research questions, particularly through individual participant data meta-analyses, as done in the Asia–Pacific region over the last decade, for instance.[13]

For such a purpose, targeting major cardiovascular diseases and risk factors seems in our opinion to be an appropriate approach and would ultimately capture the studies with relevance for the investigation of other risk factors. In the absence of individual participant data to quantify and compare the contribution of risk factors to disease occurrence, we are unable to understand what sort of classification of risk factors the authors are referring to, which incidentally, was not an aim of our study.

The time has come for the establishment of a prospective register of African cohort studies on cardiovascular and other chronic diseases in order to ensure the dissemination of valuable knowledge, the identification of research needs, and the promotion of health in the African region.

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Drug Trends in Cardiology

High patient compliance with nicacin/laropiprant in large clinical trial

Interim safety and tolerability results from HPS-2 THRIVE study released at 2012 ESC congress

Of the patients randomised to niacin/laropiprant in the HPS-2 THRIVE study, 75% remained compliant after three years of therapy with the combination of an extended-release niacin and the non-flushing agent, laropiprant.* HPS-2 THRIVE is a heart-protection study focused on treating high-density lipoprotein (HDL) cholesterol to reduce the incidence of vascular events.

It is being undertaken in both Europe and China, involving more than 25 000 patients. The clinical outcome data for the four years' follow up of the study will be available early next year.

Speaking at the ESC hotline session, Prof Jane Armitage, University of Oxford, pointed out that laropiprant, the prostaglandin D2 receptor antagonist was developed following the discovery of the DP1 receptor, which increases blood flow in the skin, causing flushes.

'The drop-out of eligible patients prior to randomisation in the niacin/laropiprant arm was 33% compared to 11% on placebo and entering the LDL-stabilisation phase.' The drop-outs in the niacin group were mainly due to muscular symptoms and the well-recognised gastrointestinal symptoms, interference in diabetes control, as well as skin reactions (flushing, itching and rashes). 'The purpose of this phase was of course to exclude patients who could not tolerate the drug', Dr Armitage noted.

In the study, the LDL cholesterol levels were well controlled (1.64 mmol/l) on background statin therapy. These were further lowered by the niacin/liropiprant treatment by 20%. HDL-C levels increased by 17%, apoplipoprotein B decreased by 14% and apolipoprotein A was increased by 16%. 'This is a very useful alteration in lipid risk', Dr Armitage noted.

Patients were recruited in China and Europe, and 80% were men, mainly with a history of coronary artery disease, and 25% had diabetes. The pre-specified safety points related to muscle and liver function, with myopathy and rhabdomyolysis being indicative of worsening kidney function. The reasons for stopping the active medication during the trial mirrored that of the pre-randomisation trial.

'It is important to note that the increase in myopathy seen in the trial has been largely driven by the higher rates among patients of Chinese ancestry, which was six-fold higher than in the Caucasian population. The majority of these cases occurred in the first year after randomisation', Dr Armitage said. 'With regard to liver function, there was very little difference between the two arms of the trial; placebo and active niacin/laropiprant therapy.

In conclusion, Dr Armitage pointed out that this is the largest trial of lipid-modification therapy to date. With regard to safety, there were no other adverse effects other than those discussed above.

*This new combination has recently been launched in South Africa by MSD.

Cardio News

New cookbook to help disarm South Africa's heart disease time bomb

Dr Vash Mungal-Singh, CEO of the Heart and Stroke Foundation South Africa (HSF), officially kicked off National Heart Awareness month with the launch of what the HSF says is another potent tool in its fight to stem the tide of cardiovascular disease, which currently claims about 200 lives in South Africa every day.

The new 'tool' is a recipe book, titled *Cooking from the Heart*, which will be distributed free to the public thanks to Pharma Dynamics, the leading provider of cardiovascular medication in the country. And there are already plans for hospitals and public institutions across South Africa to adopt its recipes and 'healthier eating' guidelines.

Cooking from the Heart is unique among healthy eating cookbooks because it contains popular and budget-friendly recipes submitted by ordinary South Africans. These have been adapted by experts to make them healthier by cutting fat, salt and sugar content while boosting nutritional value in line with the HSF's healthy eating guidelines.

Mungal-Singh says that this new initiative is the first of its kind. 'We've launched many initiatives over the years but never one quite like *Cooking from the Heart*. It offers the public a practical resource to tackle non-communicable diseases such as heart disease and stroke, which are closely linked to poor diet. We hope that everyday cooks will see how easy it is it to make healthier favourites such as potato salad or beef stew.

'Cardiovascular disease is a growing problem in South Africa as the intake of saturated and trans fats, salt and sugar is on the increase. By 2030, the United Nations predicts that deaths of South Africans aged from 35 to 64 years will have skyrocketed by 40%. Nutrition is a very important part of managing and preventing heart disease and stroke. There is a misconception that a healthy diet is expensive, impractical or unappetising. *Cooking from the Heart* will dispel that myth once and for all.'

Mariska Fouche, public affairs manager at Pharma Dynamics, says that the book will be available free of charge to members of the public who attend free screenings for heart disease risk factors at shopping centres across the country during Heart Awareness month. 'Screenings will include blood pressure, cholesterol and glucose testing and vital information about cardiovascular disease.'

Fouche says that not only will *Cooking from the Heart* help home cooks to produce more nutritious meals, it is also an excellent practical resource for healthcare practitioners (HCPs).

'Research conducted by the Medical Research Council and the Chronic Diseases Initiative in Africa with focus groups across the country found that many cardiovascular disease patients received limited advice about adapting their diets from doctors at the time of their diagnosis. They struggled to incorporate the little advice they did get into their everyday lives. This meant that they didn't make meaningful changes to their diets, which had a negative impact on the management of their condition.

'HCPs don't necessarily have the tools to teach people about healthier eating habits. This book is a vital part of the HSF's preventative toolkit to help tackle the looming heart disease and stroke epidemic in South Africa', she says.

Plans are underway for public hospitals to serve patients meals based on the nutritional guidelines and recipes contained in the book, and it is hoped that this will foster stronger awareness of the link between diet and cardiovascular disease.

Cooking from the Heart has also caught the attention of Health Minister Dr Aaron Motsoaledi, who said: 'The Department of Health commends the HSF and Pharma Dynamics for taking this bold and practical step against heart disease and stroke. The idea of researching and publishing recipes that are both economical and culturally appropriate is an excellent way of creating awareness of the need for healthier eating and is a concrete means for people in all communities to improve their overall health.'

Cooking from the Heart is available free of charge to all members of the public. To get a copy, members of the public can:

- download a free e-copy from www.cookingfromtheheart.co.za
- access www.heartrecipes.mobi on their smart phones
- go to www.heartfoundation.co.za or contact Freddie on 021 403 6450 or freddie@heartfoundation.co.za to find out about free distribution in their area
- visit the nearest Clicks Clinic to pick up one of 57 000 copies.

For a complete list of free screening dates and locations visit www.heartfoundation.co.za.

Cardiovascular Topics

Echocardiographic patterns in treatment-naïve HIV-positive patients in Lagos, south-west Nigeria

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Abstract

Introduction: **Cardiovascular abnormalities are common in HIV-infected patients, although often clinically quiescent. This study sought to identify by echocardiography early abnormalities in treatment-naïve patients.**

Methods: **One hundred patients and 50 controls with no known traditional risk factors for cardiovascular disease were recruited for the study. The cases and controls were matched for age, gender and body mass index. Both groups had clinical and echocardiographic evaluation for cardiac abnormalities, and CD_4 count was measured in all patients.**

Results: **The cases comprised 57 females (57.0%) and 43 males (43.0%), while the controls were 28 females (56.0%) and 22 males (44.0%) ($\chi^2 = 0.01$; $p = 0.913$). The mean age of the cases was 33.2 ± 7.7, while that of the controls was 31.7 ± 9.7 ($t = 1.02$; $p = 0.31$). Echocardiographic abnormalities were significantly more common in the cases than the controls (78 vs 16%; $p = 0.000$), including systolic dysfunction (30 vs 8%; $p = 0.024$) and diastolic dysfunction (32 vs 8%; $p = 0.002$). Other abnormalities noted in the cases were pericardial effusion in 47% ($\chi^2 = 32.10$; $p = 0.000$) and dilated cardiomyopathy in 5% (five); none of the controls had either complication. One patient each had aortic root dilatation, mitral valve prolapse and isolated right heart dilatation and dysfunction.**

Conclusion: **Cardiac abnormalities are more common in HIV-infected people than in normal controls. A careful initial and periodic cardiac evaluation to detect early involvement of the heart in the HIV disease is recommended.**

Keywords: HIV, cardiac abnormalities, echocardiography

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Human immunodeficiency virus (HIV) possesses an intrinsic cardiopathogenic action that may be detected in even the early stages of HIV disease.[1] The medical literature clearly documents that HIV/AIDS is a multi-systemic disease, affecting virtually every organ and system of the body, and causing progressive dysfunction.[2-3] It is an established fact that the heart is not spared in the exploits of this rampaging entity.[4-6]

Cardiovascular abnormalities are common in HIV-infected patients, although they are often clinically quiescent and frequently attributed to dysfunction in other organ systems.[7-9] Of interest is the observation that the incidence of AIDS-related heart disease found in post-mortem studies is significantly higher than the incidence of abnormalities diagnosed clinically ante mortem.[10] Therefore it is possible that many AIDS patients have cardiac abnormalities that are not recognised during the course of their illness.

In an autopsy study carried out in 1998, cardiac abnormalities were noted in two-thirds of the patients with AIDS.[11] These abnormalities, which were attributed directly or indirectly to the HI virus and/or treatment side effects, could largely have been detected early ante mortem using echocardiography, a non-invasive, radiation-free investigation.[10,12,13]

Cardiac involvement impacts on the natural history and prognosis of the HIV disease. This demands an awareness by clinicians of its cardiovascular manifestations for a complete and rational diagnosis and management.[5] This study sought to identify echocardiographic abnormalities in treatment-naïve patients in order to assess the cardiac effects of HIV infection, while excluding drug effects.

Methods

This was a descriptive, cross-sectional study of 100 patients with HIV infection recruited via the HIV clinic of the Lagos University Teaching Hospital (LUTH), Lagos, Nigeria. The patients were yet to commence antiretroviral therapy. The cohort was made up of HIV-infected individuals referred to, or identified in the clinic. They had no prior history of cardiac disease, and were not previously diagnosed as hypertensive or diabetic. Those with a history of use of illicit drugs or previous treatment with drugs with cardiotoxic effects were excluded.

Fifty healthy, HIV-negative individuals served as controls. They were recruited after voluntary screening in the HIV clinic side laboratory to confirm their negative status. Other exclusion criteria for the HIV-positive patients were also applicable in the control group. They were recruited to match the age, gender and body mass index (BMI) profile of the HIV cases.

The research was carried out in accordance with the Declaration of Helsinki. The study protocol was explained to all participants and they gave their informed consent. Approval for the study was obtained from the local Ethics Committee in the institution.

Patients and controls underwent thorough clinical evaluation with an emphasis on the cardiovascular system. Venous blood was collected from all HIV-infected patients for lymphocyte typing to obtain the CD_4 cell count.

Transthoracic echocardiography was performed using a Siemens Sonoline S1-450 in the cardiovascular laboratory with a 3.5-MHZ transducer probe. Each subject was briefed on the non-invasive nature of the procedure to allay fear and anxiety. Two-dimensional (2D), M-mode, pulse-wave, continuous-wave and colour Doppler echocardiography assessment was done with the subject in the left lateral decubitus position.[12] The two-dimensional images were obtained in the parasternal long- and short-axis views, apical and subcostal views.[12,13]

Left atrial diameter (LA), aortic size (AO), right ventricular outflow tract (RVOT), left ventricular end-systolic (LVEDs) and end-diastolic (LVEDd) diameters, interventricular septum (IVS), left ventricular posterior wall (LVPW), estimated right ventricle (ERV), and end-point septal separation (EPSS) measurements were obtained from 2D directed, M-mode recordings from the parasternal long axis.[13] Measurements were taken (in cm) according to the American Society of Echocardiography guidelines (leading-edge methodology).[14] The mean of three measurements was recorded.

Doppler studies included pulmonary velocity (PV), aortic velocity (AV), transmitral flow, and deceleration time (DT) measurements. Isovolumetric relaxation time (IVRT) was obtained from pulse-wave Doppler studies.[13] Echocardiographic abnormalities, e.g. pericardial effusion, thickening, separation, valvular lesions such as stenosis, and regurgitations and regional wall-motion abnormalities were also looked for.

The following definitions were used: dilated left ventricle refers to LVEDd > 5.2 cm.[13] Left ventricular systolic dysfunction was determined by left ventricular fractional shortening (LVFS) < 28%.[9,15,16] The fractional shortening was computed from the basic linear measurements using an appropriate formula:[15]

$$\text{LVFS} = \frac{(\text{LVEDd} - \text{LVEDs})}{\text{LVEDd} \times 100}.$$

The severity of LV dysfunction was graded based on the recommendation by the ESC:[15] mild dysfunction, fractional shortening = 22–27% ; moderate = 17–21%; severe < 16%. The ejection fraction was calculated using the formula:[15]

$$\text{EF} = \frac{\text{LVEDV} - \text{LVESV}}{\text{LVEDV} \times 100}$$

where LVEDV (left ventricular end-diastolic volume) = LVEDd^3, and LVESV (left ventricular end-systolic volume) = LVEDs^3. Dilated cardiomyopathy was diagnosed using three criteria: left ventricular end-diastolic diameter (LVEDd) > 5.5 cm,[16-18] global hypokinesia, and fractional shortening (LVFS) < 28%.[16,19]

Isolated right heart dilatation: right ventricle and atrium larger than left ventricle and atrium, respectively on standard two-dimensional echocardiography in apical view; right ventricular end-diastolic dimension > 3.0 cm with normal left ventricular size and function.[18,20]

Left ventricular diastolic dysfunction was diagnosed in the presence of any of the following criteria:[21]

- impaired relaxation with an E/A ratio < 1, IVRT > 100 ms and DT > 220 ms
- pseudonormalisation resembling the normal trans-mitral configuration with regard to the mitral inflow but with normal or low DT
- restrictive pattern with E/A ratio > 2, IVRT < 70 ms and DT < 160 ms.

Pericardial effusion refers to an echo-free space behind the left ventricle with or without an anterior echo-free space. The size of the pericardial effusion was defined as follows: small when the maximum pericardial space at end-diastole was < 1.0 cm, moderate when the space was ≥ 1.0 cm but < 2.0 cm, and massive/severe when the pericardial space was ≥ 2.0 cm between the pericardial layers.[22,23]

Results

A total of 100 HIV-positive cases and 50 healthy control subjects were recruited for the study. The cases comprised 57 females (57.0%) and 43 males (43.0%), while the controls included 28 females (56.0%) and 22 males (44.0%). The gender distribution was comparable ($\chi^2 = 0.01$; $p = 0.913$). The mean age and BMI were not statistically different.

The most common symptoms relevant to the heart were cough (23%), palpitations (11%) and shortness of breath (7%). Most were, however, non-specific as many of the patients had associated anaemia, infections and pulmonary disease, which could have accounted for these symptoms. Only two patients had overt symptoms of heart failure (dyspnoea at rest, orthopnoea, paroxysmal nocturnal dyspnoea, leg swelling, tender hepatomegaly), while one had features of massive pericardial effusion. All three had a CD_4 count less than 100/µl.

The mean pulse rate was significantly higher in the cases than the controls (87.04 ± 13.04 and 78.56 ± 6.22, respectively; $p = 0.000$) (Table 1). There was no significant difference between the systolic blood pressure (SBP) of the cases and controls. The diastolic blood pressure (DBP) of the cases was, however, significantly lower than that of controls (70.59 ± 7.39 and 74.60 ± 7.27, respectively; $p = 0.002$).

The CD_4 count ranged from 7.00 to 1 481.0/µl with a mean of 232.0 ± 214.8/µl.

TABLE 1. DEMOGRAPHIC AND CLINICAL FEATURES OF THE STUDY POPULATION

Features	*Cases (n = 100)*	*Controls (n = 50)*	*t*	*p*
Age (years)	33.20 ± 7.67	31.72 ± 9.71	1.016	0.311
BMI	21.41 ± 4.35	22.56 ± 2.76	2.890	0.091
BSA (m^2)	1.66 ± 0.19	1.68 ± 0.17	0.508	0.612
Pulse rate (beats/min)	87.04 ± 13.04	78.56 ± 6.22	4.348	0.000*
DBP (mmHg)	70.59 ± 7.39	74.60 ± 7.27	3.146	0.002*
SBP (mmHg)	111.56 ± 11.53	113.00 ± 12.98	0.687	0.493

Values are mean ± SD. BMI: body mass index; BSA: body surface area; DBP: diastolic blood pressure; SBP: systolic blood pressure. SD: standard deviation; *$p < 0.05$ is statistically significant.

TABLE 2. ECHOCARDIOGRAPHIC DIMENSIONS IN CASES AND CONTROLS

Parameters	*Cases (n = 99)*	*Controls (n = 50)*	*t*	*p*
LA (cm)	2.94 ± 0.51	2.96 ± 0.39	0.201	0.841
AO (cm)	2.71 ± 0.45	2.60 ± 0.38	0.999	0.319
RVOT (cm)	2.85 ± 0.41	2.95 ± 0.49	1.316	0.190
ERV (cm)	2.11 ± 0.43	1.91 ± 0.30	2.937	0.004*
IVS (cm)	0.97 ± 0.19	0.93 ± 0.17	1.414	0.160
LVPW (cm)	0.83 ± 0.15	0.84 ± 0.17	0.155	0.877
LVEDd (cm)	4.58 ± 0.58	4.50 ± 0.53	0.816	0.416
LVEDs (cm)	3.23 ± 0.54	2.99 ± 0.46	2.712	0.008*
LVEDd/BSA (cm/m^2)	2.77 ± 0.35	2.69 ± 0.29	1.412	0.160
LVMI (g/m^2)	84.33 ± 24.68	78.72 ± 23.81	42.87	0.000*
RWT	0.37 ± 0.08	0.38 ± 0.08	0.151	0.881

Values are mean ± SD. LA: left atrial diameter; AO: aortic root diameter; AOEX: aortic excursion; RVOT: right ventricular outflow tract; ERV: estimated right ventricular diameter; IVS: interventricular septum; LVPW: posterior wall thickness; LVEDd: left ventricular end-diastolic diameter; LVEDs: left ventricular end-systolic diameter; BSA: body surface area.
*$p < 0.05$ is statistically significant.

Of the 100 cases studied, 99 had cardiac chamber dimension measurements taken. One did not because a large pericardial effusion precluded accurate measurements. Comparison of the echocardiographic dimensions between the cases and the controls is summarised in Table 2.

HIV-positive patients had significantly increased LVEDs, ERV and LVMI compared with the controls. Although the LVEDd was higher in the cases, it did not reach the level of statistical significance. However left ventricular dilatation, defined as LVEDd > 5.2 cm, was significantly more in the cases than the controls ($p = 0.03$).

Comparison of left ventricular systolic and diastolic functions is summarised in Table 3. The cases had significantly reduced systolic parameters (LVFS, LVEF) and significantly increased IVRT, an important diastolic parameter, compared with the controls.

Echocardiographic abnormalities were found in 78% of the cases overall compared with 16% in the controls ($\chi^2 = 52.38$; $p = 0.000$). The echocardiographic abnormalities are summarised in Table 4.

TABLE 3. SYSTOLIC AND DIASTOLIC PARAMETERS IN CASES AND CONTROLS

Parameters	*Cases (n = 99)*	*Controls (n = 50)*	*t*	*p*
SV	63.91 ± 24.90	66.19 ± 22.92	0.54	0.589
LVEF	64.45 ± 8.63	70.17 ± 7.08	4.05	0.000*
LVFS	29.60 ± 5.60	34.51 ± 14.61	2.95	0.004*
DT (ms)	187.82 ± 30.45	181.04 ± 16.23	1.48	0.142
IVRT(s)	88.24 ± 19.62	80.81 ± 10.81	2.48	0.015*
E	75.05 ± 16.77	77.71 ± 16.59	0.92	0.36
A	50.20 ± 11.25	51.51 ± 11.29	0.67	0.50
E/A	1.56 ± 0.49	1.55 ± 0.33	0.02	0.89
EPSS	0.45 ± 0.31	0.34 ± 0.22	2.11	0.04*

Values are mean ± SD. SV: stroke volume; LVEF: Left ventricular ejection fraction; LVFS: left ventricular fractional shortening; DT: deceleration time; IVRT: isovolumic relaxation time. E: early diastolic filling; A: atrial contraction; E/A: ratio of early (E) to late (A) diastolic filling velocities in the mitral inflow; EPSS: endpoint septal separation.
*$p < 0.05$ is statistically significant.

Of the 100 cases studied, 30 (30%) had systolic dysfunction compared with four of the 50 controls (8%), $p = 0.004$. Twenty-five (83%) of these had mild dysfunction, while five (17%) had moderate to severe dysfunction. Of the 25 patients who had mild systolic dysfunction, 17 (68%) had a CD_4 count less than 200/µl, while eight (32%) had a CD_4 > 200/µl. All five (17%) with moderate to severe systolic dysfunction had a CD_4 count < 200/µl. There was no regional wall-motion abnormality in the cases.

Furthermore, 32 (32%) of the cases had diastolic dysfunction compared with four of the controls (8%), $p = 0.002$. Of these, six (19%) had impaired relaxation; 10 (31%) had pseudonormalisation pattern, while the remaining 16 (50%) had restrictive diastolic dysfunction. Of the cases that had either pseudonormalisation or restrictive diastolic dysfunction, 15 (58%) had CD_4 counts < 200/µl, while the remaining 11 (42%) had CD_4 > 200/µl.

Five (5%) of the cases and none of the controls had dilated cardiomyopathy ($p = 0.169$), while one of the cases had isolated right-sided dilatation. One of the cases also had aortic root dilatation with severe regurgitation, while another had mitral valve prolapse.

Pericardial involvement was common in the cases. Of the 100 cases, 47 (47%) had pericardial effusion, while none had this in the control group (Table 4). This difference was strikingly significant ($p = 0.000$). In patients with pericardial effusion, 39 had mild effusion while eight had moderate to severe effusion, with a mean CD_4 cell count of 125/µl (Fig. 1).

All five patients with dilated cardiomyopathy (DCM) had a CD_4 count < 200/µl. The mean CD_4 of those with DCM was 80/µl. The only patient with isolated right-sided dilatation had a CD_4 count of 67/µl.

Discussion

This study clearly reveals that the majority of patients with HIV infection had echocardiographic abnormalities which were clinically quiescent. This suggests echocardiography as a relevant tool for diagnosis of sub-clinical cardiac abnormalities, with the aim of instituting management early where necessary. Similar findings have been reported by other workers.[9,24,25]

Our study shows that pericardial effusion was frequently seen in our HIV-infected patients, with a spectrum ranging from asymptomatic mild effusion to severe pericardial

TABLE 4. ECHOCARDIOGRAPHIC ABNORMALITIES IN CASES AND CONTROLS

Echocardiographic abnormalities	*Cases (n = 99)*	*Controls (n = 50)*	χ^2	*p*
Pericardial effusion*	47 (47.00)	0 (0)	32.10	0.000
Systolic dysfunction	30 (30.30)	4 (8)	8.16	0.004
Diastolic dysfunction	32 (32.32)	4 (8)	9.44	0.002
Dilated left ventricle	15 (15.15)	1 (2)	4.70	0.031
Dilated cardiomyopathy	5 (5.05)	0 (0)	1.29	0.169
Isolated right-sided dilatation	1 (1.01)	0 (0)	0.12	1.000
Aortic root dilatation	1 (1.01)	0 (0)	0.12	1.000
Mitral valve prolapse	1 (1.01)	0 (0)	0.12	1.000

Values are number (%). *$n = 100$ cases for pericardial effusion.

effusion. Pericardial disease is the most frequent cardiovascular manifestation of HIV infection[24,25] and it is often associated with shortened survival, independent of CD_4 count and serum albumin values.[23,26,27] The prevalence of pericardial disease on echocardiography in Prendergast's study ranged from 10 to 59%,[2] although the majority of these patients were asymptomatic. This was confirmed by our findings, where pericardial effusion was found in almost half of the patients, while only one patient had overt symptoms. With the increasing incidence of HIV infection, pericardial effusion and its attendant complications may become a major cardiac abnormality to contend with in future.

No definitive cause was determined for any pericardial effusion in this study. Determination of the aetiology of pericardial effusions in HIV-infected patients is often difficult.[22,23,26] Pericardiocentesis is not feasible in the majority of these patients because most pericardial effusions are small,[22,23,28] and even when indicated for the relief of tamponade, its diagnostic accuracy is said to be low.[29]

Various causative factors involved in the development of pericardial disease have been described. Tuberculosis is the commonest cause of pericardial disease in Africa,[26,27] accounting for 86 to 100% of cases.[29] Other reported causative factors include the human immunodeficiency virus itself,[2,30] opportunistic infections such as cytomegalovirus,[31] mycobacterium,[32] cryptococcus,[33] bacterial infections,[34] malignancies such as Kaposi's sarcoma,[35] and non-Hodgkin lymphoma.[22,36] It can also be part of a generalised effusive serous process involving pleural and peritoneal surfaces, which is probably a consequence of enhanced cytokine expression.[4,22]

The findings in this study also confirm that HIV infection was associated with left ventricular dysfunction and increased ventricular dimensions. Similar trends have been noted in other studies.[9,18,34-36] The presence of ventricular dysfunction in the absence of chamber enlargement, as found in about half of those with ventricular dysfunction in our study, has also been reported in other studies.[10,24,28] This has been posited to represent an early phase of heart muscle disease/cardiomyopathy, from which the patients eventually progress to left ventricular dilatation and dilated cardiomyopathy.[20,24,28]

Systolic dysfunction, which is a frequently documented finding in echocardiography of HIV-infected patients,[9,10,28,37,38] was noted in about a third of our cases, signifying reduced myocardial contractility. The dysfunction was more frequent with disease progression, paralleling the reports by other workers.[9,10,28,37] Systolic dysfunction is said to be an important cause of morbidity and mortality in AIDS patients.[38] It is also posited that symptomatic heart failure will occur in approximately 6% of these patients, especially at the end stage of the disease.[26,35,39] With this in mind, early recognition of dysfunction and institution of management may impact on the overall outcome of these patients.[9]

Diastolic dysfunction was also noted in our patients, signifying ventricular filling abnormalities due to a non-compliant ventricle.[21] Diastolic dysfunction was also observed to be more frequent and worsening with disease progression. The findings in our study compare with the 30% prevalence noted by Danbauchi *et al*.[25] in their work. Diastolic dysfunction has also been reported in other studies.[16,37]

DCM is a well-documented cardiac abnormality in HIV/AIDS,[9,34,40,41] and was found in 5% of our cases, with none in the control group (Fig. 2). All patients with DCM had more advanced immunosuppression with a mean CD_4 count of 80/µl. This result correlates well with several reports that dilated cardiomyopathy in HIV is associated with advanced immunosuppression and lower CD_4 lymphocyte counts < 100/µl.[3,9,18,28,29] Nzuobotane *et al*.[9] demonstrated a similar relationship between the degree of immunosuppression and the likelihood of cardiomyopathy. Interestingly, a CD_4 count of 100/µl proved to be the important threshold in that study as well. Currie *et al*.[18] in a similar study, reported DCM in 4% of cases, a result which parallels that of

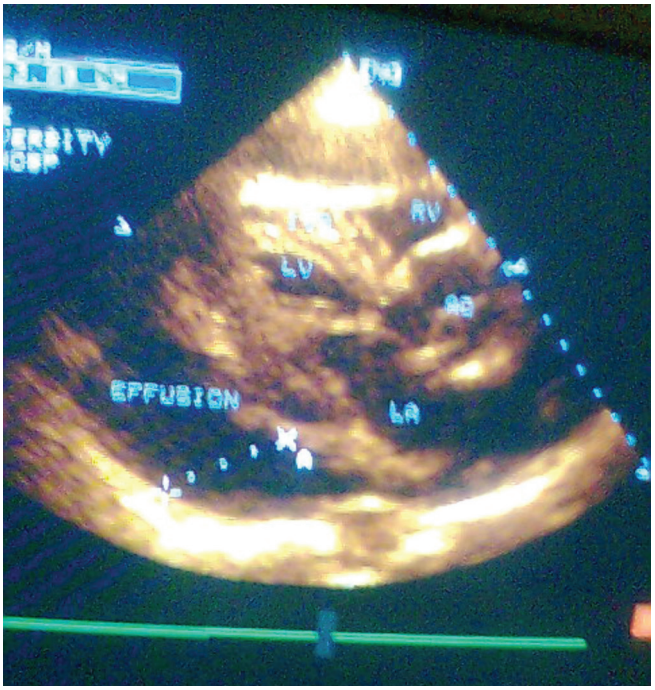

Fig. 1. Massive pericardial effusion in a patient with HIV/AIDS, shown from the pasternal long-axis view.

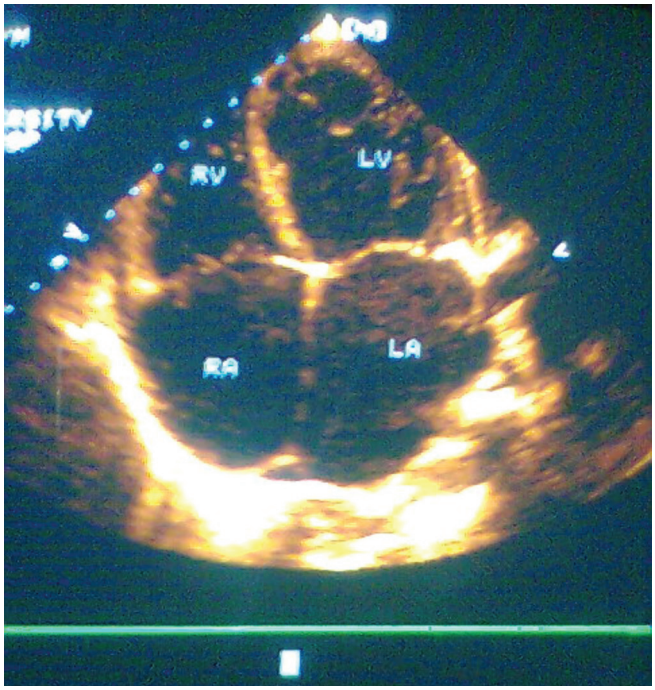

Fig. 2. Apical four-chamber view showing dilated cardiomyopathy.

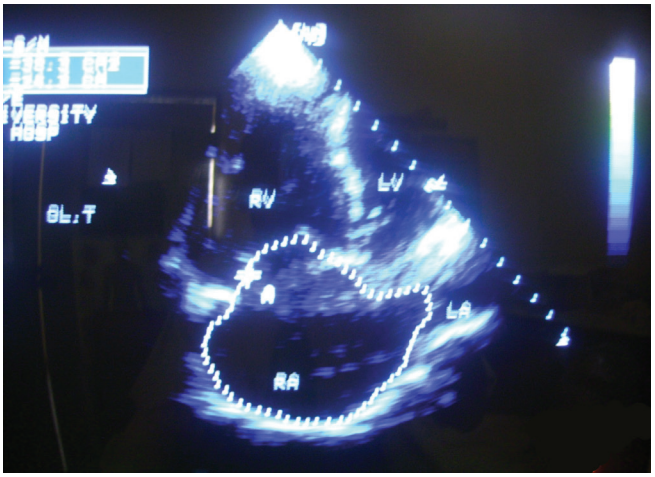

Fig. 3. Apical four-chamber view showing isolated right ventricular and atrial dilatation. Note the significantly enlarged right ventricle and right atrium, compared with the small left ventricle and left atrium.

our study. In their study DCM was also strongly associated with advanced immunosuppression.

No definitive aetiologies were determined for heart muscle disease in our study. The aetiopathogenesis of cardiomyopathy remains unclear, often multifactorial.[3,29,34,42] Myocarditis and direct HIV invasion of myocardial tissue are the most studied causes of dilated cardiomyopathy in HIV infection.[2,5,6,42] Co-infection with other cardiotropic viruses such as Coxsackie virus, cytomegalovirus and Epstein-Barr virus have also been reported.[3,5,6,34,43]

Other causes include the cardiotoxic effect of antiretroviral drugs such as zidovudine,[26,34,44] autoimmunity,[3,25,45,46] and nutritional factors such as deficiency of selenium and other trace elements.[3,5,7,17,47] Selenium deficiency as a cause of HIV-related heart muscle disease may be of considerable interest in Africa[9] and in our study, considering that most of these patients present with multiple nutritional deficiencies, prolonged diarrhoea and wasting, which may involve selenium deficiency.[9] Selenium supplementation has been shown to improve cardiac dysfunction in these patients.[2,4,5,7,17]

Isolated right heart dilatation with dysfunction was found in one of the patients in our study, who had significant pulmonary disease of over six months' duration (Fig. 3). The very low CD_4 count of 64/µl in this patient suggested some relationship with severe disease progression, as reported in other studies as well.[18,20]

One of the patients in our study, with a CD_4 of 171/µl, had aortic root dilatation, which was associated with severe aortic regurgitation (Fig. 4). Although not common, aortic root dilatation and even aneurysm has been reported in other studies.[20,48] This may be the beginning of large-vessel vasculitis of possible infective or immune-complex origin, involving the aorta and its major branches, which has been reported by other workers.[49,50]

Our study did not evaluate other possible co-morbidities, such as HIV-associated nephropathy and anaemia, which may be present in the patients aside from cardiovascular abnormalities. We also could not use newer methods, such as tissue Doppler, to assess diastolic function. This was unfortunate because tissue Doppler is more reliable than the method used in our study, it helps to clarify the issue of pseudonormalisation, and it is less load-dependent. Furthermore, we could not assess the prognostic implications of cardiovascular involvement in our subjects.

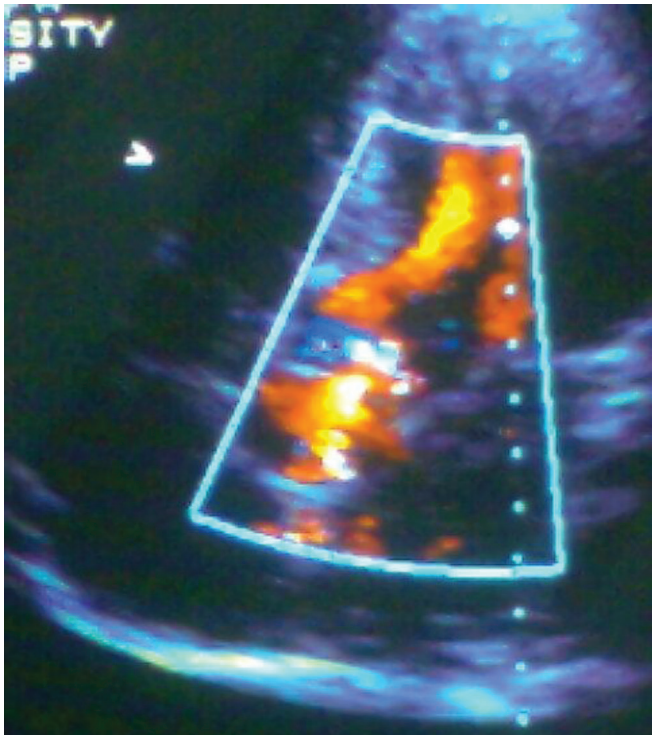

Fig. 4. Apical five-chamber view of one of the patients with a dilated aortic root, showing moderate to severe aortic regurgitation. Note the red flame from the middle (aortic ring) extending towards the apex of the left ventricle.

Conclusion

In view of the high frequency of cardiac abnormalities detected by echocardiography in the HIV/AIDS patients in our study, it is suggested that HIV-positive patients should have a careful initial and periodic cardiac evaluation to detect early involvement of the heart in the HIV disease.

We thank Dr Oridota for useful advice and statistical input, Matron Bastos, Mr Hakeem and all members of staff of the HIV clinic in LUTH for their support and encouragement throughout this work.

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Case Report

An unusual embolic complication of percutaneous coronary artery intervention and simple percutaneous treatment

ERKAN ILHAN, ÖZER SOYLU, TOLGA S GÜVENÇ, YIĞIT ÇANGA, MEHMET ERGELEN

Abstract

Emboli are among the most feared complications of interventional cardiology. Although surgery is needed in most cases for the removal of peripheric foreign body emboli, some may be extracted by percutaneous intervention. We present a case of retrieval of a femoral sheath fragment via contralateral femoral access, wiring of the sheath fragment, and retrieval with an 'anchoring balloon' system.

Keywords: percutaneous coronary intervention, femoral sheath, peripheric embolus

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Case report

A 59-year-old male with a history of hypertension and diabetes mellitus was admitted to our emergency department with non-ST-segment elevation myocardial infarction. After medical treatment and stabilisation of the patient, coronary angiography was performed from the right femoral artery with a 6F sheath (Sentia, Ayra Medical, Turkey).

Drug-eluting stent implantation to the critical left anterior descending coronary artery lesion was attempted. Unfortunately the procedure was aborted because of unsuccessful percutaneous coronary intervention (PCI), and bypass surgery was planned. Since intravenous heparin had been used during PCI, removal of the sheath was planned after six hours.

During removal of the sheath, we noticed that the back-bleed valve and side-arm connector of the sheath had detached from the shaft. After removal of the valve and side arm, homeostasis was obtained with manual pressure and the patient was transferred to the catheter laboratory to visualise the exact position of the shaft.

Under fluoroscopy, the shaft was visualised in the right femoral artery (Fig. 1). Percutaneous removal of the shaft from the contralateral femoral artery was planed. After insertion of a 7F sheath (St Jude Medical, Minnetonka, USA) into the left femoral artery, a 7F left Judkins guiding catheter (Boston Scientific, Mexico) was advanced into the right external iliac artery.

When the shaft and the catheter were adjacent, a 0.014-inch guidewire was passed through both lumens (Fig. 2A). A 2.5 ×

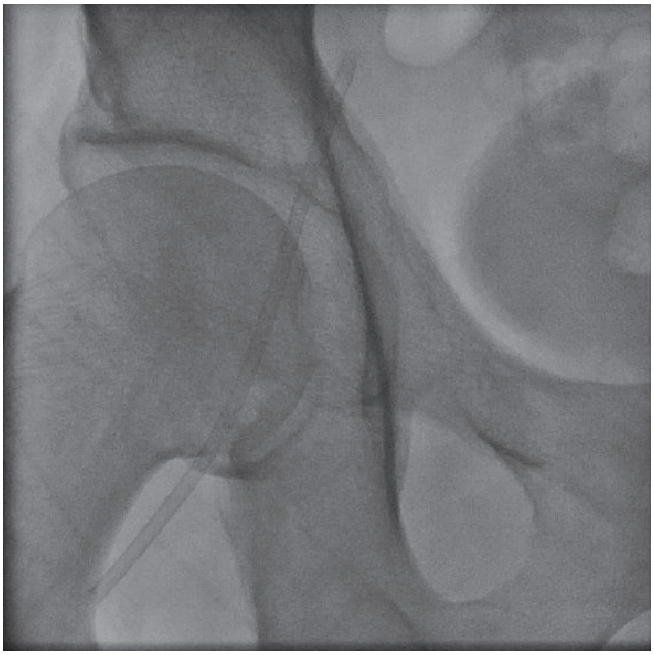

Fig 1. Shaft of the sheath in the right femoral artery, seen under fluoroscopy.

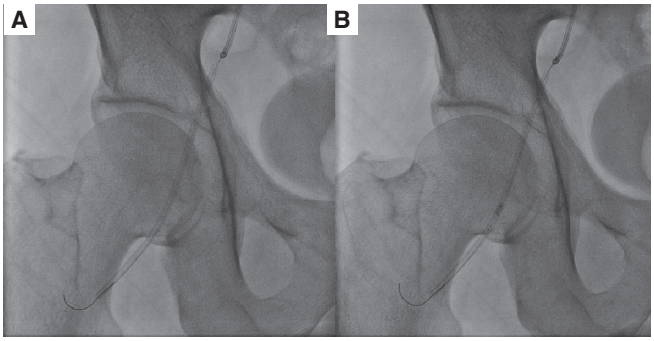

Fig. 2. A 0.014-inch guidewire passed through both lumens (A) and a 2.5 × 15-mm angioplasty balloon was inflated within the shaft.

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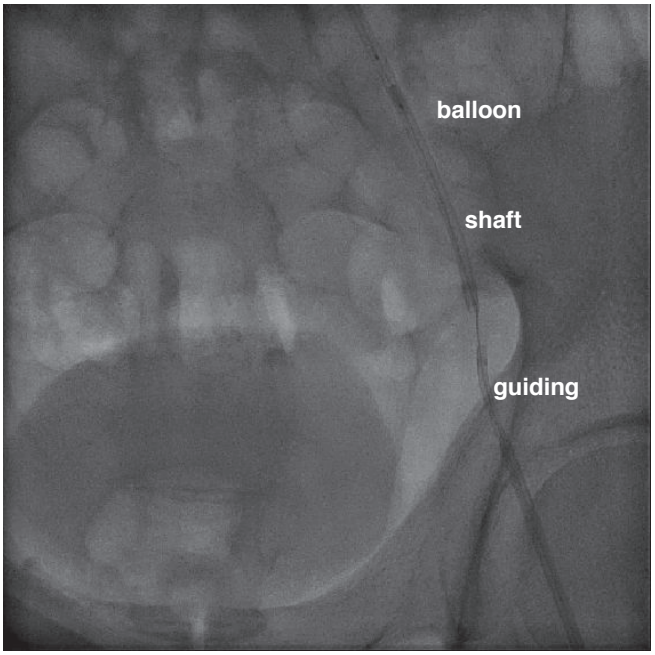

Fig. 3. The shaft was moved to the left femoral artery with the help of the inflated balloon within it.

15-mm angioplasty balloon was placed into the shaft and inflated to its rated bursting pressure (Fig. 2B). The system as a unit (catheter, balloon and broken shaft) was eased back. When the broken shaft arrived at the tip of the left femoral artery sheath (Fig. 3), the vascular surgeon made a small incision through the skin and into the left femoral artery. The shaft and inflated balloon were removed and the surgeon repaired the femoral artery.

The patient was discharged from hospital after coronary artery bypass grafting without any complication related to the percutaneous procedure.

Discussion

Various percutaneous retrieval devices have been developed for intravascular foreign bodies and have been used successfully for many years.[1–5] Most foreign bodies are defined as catheter fragments, guidewires, stents, pace leads, vena cava filters and cardiac valve fragments.[1–3] However, to the best of our knowledge this is the first case in the literature of a part of the arterial sheath embolising shortly after vascular intervention.

We used a 7F sheath, which was the largest available in our catheter laboratory at that time, for the contralateral femoral artery. Another method would have been to insert a new, larger sheath via the ipsilateral femoral artery and using the same method, the removal might have been easier with a single arterial access. However, in our case, location of the sheath fragment necessitated a too-high or too-low ipsilateral femoral artery puncture, so we did not use the ipsilateral access.

This was a simple procedure, and at least two sizes larger French sheathes could be used to remove such foreign bodies percutaneously without surgical consultation.

Conclusion

Retrieval devices such as snares and forceps should be the standard percutaneous treatment modality for endovascular foreign body retrieval. However, if retrieval is not possible within a short time, the above method could be used for selected patients before surgical consultation.

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Case Report

Anomalous left coronary artery arising from the pulmonary artery

M DURAND, ET NGUYEN, AM CREAN

Abstract

A 24-year-old female presented to her general practitioner with shortness of breath. She was referred for an echocardiogram, which demonstrated features suggestive of a right coronary artery fistula, and referred to our institute. We performed a contrast-enhanced, prospectively triggered cardiac CT angiogram, which demonstrated the primary and secondary features of anomalous left coronary artery arising from the pulmonary artery (ALCAPA), also known as the Bland–White–Garland syndrome, a rare congenital abnormality of the origin of the left main coronary artery.

Keywords: anomalous left coronary artery arising from the pulmonary artery, ALCAPA, congenital coronary abnormality

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DOI: 10.5830/CVJA-2012-031

A 24-year-old female presented to her general practitioner with shortness of breath. She was referred for an echocardiogram, which demonstrated features suggestive of a right coronary artery fistula, and she was referred to our institute. We performed a contrast-enhanced, prospectively triggered cardiac CT angiogram, using the low-dose 100-kVp technique. Using a 320 multi-detector row scanner (Aquilion One, Toshiba Medical Systems, Japan), a volumetric acquisition in late diastole was performed in a single heartbeat.

The three-dimensional volume-rendered virtual image (Fig. 1) and reformatted maximum-intensity projection image (Fig. 2) demonstrate the left main coronary artery arising from the left infero-lateral aspect of the main pulmonary artery. The left main coronary artery extends towards the interventricular groove and branch into the left anterior descending and left circumflex coronary arteries. The right coronary artery (RCA) had the conventional origin from the right coronary sinus of valsalva.

All the coronary arteries were significantly dilated with multiple intercoronary (Fig. 3) and septal (Fig. 4) collateral vessels, as seen on the maximum-intensity projection images. The left ventricle was significantly dilated (not shown) as a result of the long-term steal of blood from the ascending aorta via the RCA, to the septal collaterals, into the anomalous left coronary system and then to the pulmonary bed and left ventricle.

The cardiac CT scan demonstrates the primary and secondary features of anomalous left coronary artery arising from the pulmonary artery (ALCAPA), also known as the Bland–White–Garland syndrome, a rare congenital abnormality of the origin of the left main coronary artery. This abnormality results in a coronary steal phenomenon, with right-sided coronary blood

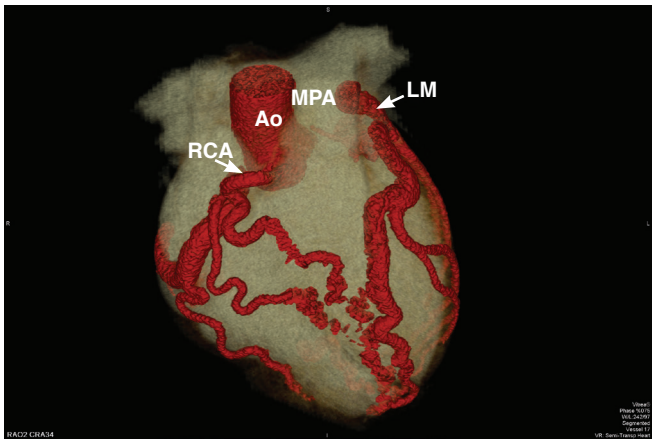

Fig. 1. Thee-dimensional volume-rendered image demonstrating the left main coronary artery (LM) arising from the main pulmonary artery (MPA). The right coronary artery (RCA) has a conventional origin from the aorta (Ao).

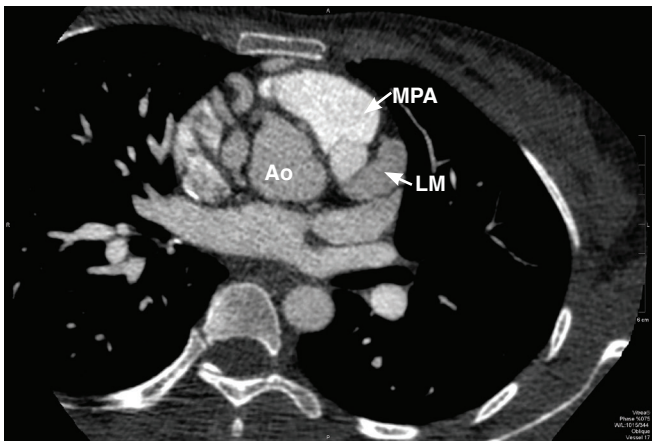

Fig. 2. Reformatted maximum-intensity projection image in the axial plane demonstrating the left main coronary artery (LM) arising from the infero-lateral aspect of the main pulmonary artery (MPA).

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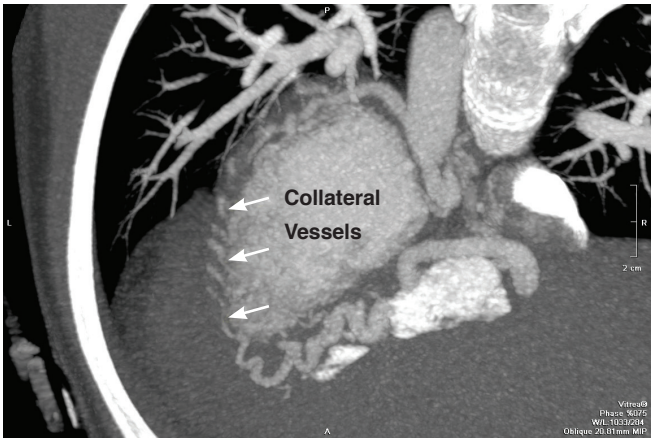

Fig. 3. Reformatted maximum-intensity projection image reconstructed in an oblique plane demonstrating multiple intercoronary collateral vessels.

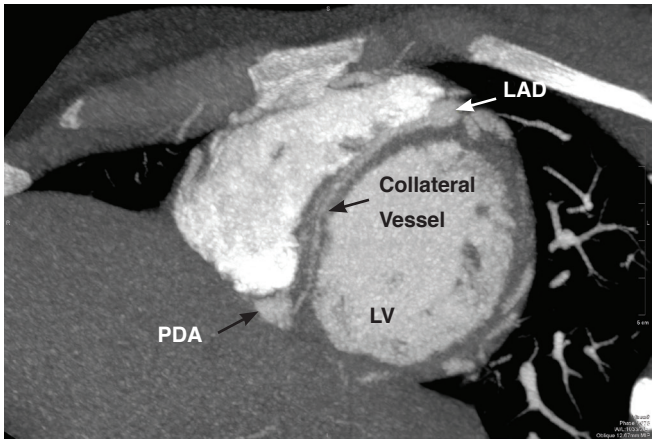

Fig. 4. Reformatted maximum-intensity projection image reconstructed in a short-axis plane demonstrating a large septal collateral vessel. Left ventricle (LV).

flow being shunted away from the myocardium and into the low-pressure pulmonary artery.

ALCAPA is one of the most common causes of myocardial infarction in children, and an initial presentation with ischaemic mitral regurgitation within the first few weeks of life is well described. However with a well-established collateral circulation, these patients may sometimes present only in adulthood. When this occurs, surgical re-implantation or bypass of the left main coronary system is usually recommended.

Case Report

A case of unexplained cyanosis

PRASHILLA SOMA, SHIRAZ ELLEMDIN

Abstract

It is now clear that hepatopulmonary syndrome (HPS) may occur and contribute significantly to gas exchange abnormalities in the setting of other cardiopulmonary abnormalities. Since there is no gold-standard diagnostic test for HPS, diagnosis rests on documenting arterial oxygenation abnormalities resulting from intrapulmonary vasodilatation in the setting of liver disease. Retrospective studies suggest that many patients with HPS develop progressive intrapulmonary vasodilatation over time and that mortality is significant. This case highlights the clinical value in investigating for HPS and right-to-left shunts when confronted with a patient presenting with unexplained hypoxia in combination with platypnoea and/or orthodeoxia.

Keywords: cyanosis, hepatopulmonary syndrome, hypoxaemia

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Case report

A 26-year-old female presented to our casualty department in March 2004 with the main symptom of progressive dyspnoea in the absence of orthopnoea or paroxysmal nocturnal dyspnoea, with associated marked impaired effort tolerance and generalised weakness. The onset of symptoms coincided with a vague episode of blunt chest trauma. There was no chest pain or palpitations. She further reported being blind in the right eye. Her past medical history included surgical removal of a non-functional pituitary macro-adenoma eight years previously, with insertion of a ventriculo-peritioneal (V-P) shunt and post-surgical radiotherapy.

On general examination, her height was 146 cm with minimal secondary sexual characteristics. Her vitals included a temperature of 37°C, blood pressure of 93/62 mmHg, pulse of 80 beats/minute, respiratory rate of 18 breaths/minute, with central and peripheral cyanosis. It was also noted that she was less dyspnoeic and cyanotic in the supine position. Auscultation of the chest revealed normal breath sounds with a physiologically split second heart sound. She was blind in the right eye with a pale optic disc and visual field defects in the left eye.

Investigations for the cyanosis included a blood gas, the results of which are shown in Table 1, a ventilation perfusion scan, chest radiograph, high-resolution CT chest and pulmonary arteriogram, all of which were normal. The echocardiogram showed normal cardiac function with normal chamber sizes and no shunts. The polysomnogram performed revealed no abnormalities. In addition, a 100% oxygen shunt study was done, which suggested a 15.4% shunt, the details of which are illustrated in Table 2. Lung functions could not be done due to poor co-operation from the patient.

In view of the platypnoea and orthodeoxia, transthoracic and transoesophageal echocardiograms were performed. Both revealed an interatrial shunt in the supine position within three cardiac cycles of injecting. The transthoracic echocardiogram was diagnostic for the sitting position as well. A final diagnosis of patent foramen ovale with right-to-left shunting was established despite normal intracardiac pressures.

The patient underwent open-heart surgery on 22 April 2004 for the closure of an alleged patent foramen ovale. However, no intracardiac shunt or anomalous drainage could be defined at cardiac surgery. She died at home on 8 May 2004 while recovering from surgery.

A post mortem was performed on 11 May 2004. The major finding consisted of a thrombo-embolus lodged deep within the right pulmonary artery. In addition, multiple small thrombi were noted adhered to the right atrial wall. The thrombus had developed in the area of the previous surgery, from where it gave origin to the thrombo-embolism that had caused the patient's sudden death.

A further finding was a massive right-sided pleural effusion

TABLE 1. RESULTS OF THE ARTERIAL BLOOD GAS IN DIFFERENT POSITIONS

Room air	*Sitting*	*45 degrees*	*Supine*
Oxygen saturation (%)	69	81	83
Partial pressure oxygen (mmHg)	26	31	35
Partial pressure carbon dioxide (mmHg)	17	19	20

TABLE 2. RESULTS OF 100% OXYGEN SHUNT STUDY

Arterial blood gas	*Oxygen saturation (%)*	*Partial pressure oxygen (mmHg)*	*Partial pressure carbon dioxide (mmHg)*	*Bicarbonate (mmol/l)*
Room air	56	33	23	13
40% oxygen	78	47	24	13
100% oxygen	99	379	22	13

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(1 000 ml). Effusions were also noted within the left thoracic cavity (200 ml), pericardium (350 ml) and peritoneum (500 ml).

The other major finding at post mortem was the presence of a small fatty liver. Histology revealed the presence of cirrhosis, with prominent fibrotic bands. After extensive special stains, the diagnosis was cryptogenic cirrhosis.

The lungs appeared to be within normal limits at post mortem, but histology revealed prominent dilatation of the vasculature of both lungs, consistent with the hepatopulmonary syndrome. Examination of the brain and endocrine systems confirmed the clinical findings.

Discussion

Platypnoea (dyspnoea induced by the upright position and relieved by recumbency) and orthodeoxia (arterial deoxygenation accentuated by the upright position and improved during recumbency) is a rare and poorly understood syndrome of orthostatic accentuation of a right-to-left shunt, usually across a patent foramen ovale.[1] Another unusual condition involving right-to-left shunting, while usually chronic, can present in a very similar fashion to right-to-left interatrial shunt, i.e. with hypoxaemia, platypnoea, orthodeoxia and a positive bubble contrast echocardiograph; hepatopulmonary syndrome (HPS).[2]

HPS is defined as the triad of liver disease, pulmonary gas exchange abnormalities leading to arterial deoxygenation, and widespread pulmonary vascular dilatation.[3] The hallmark of pulmonary vascular changes in HPS are dilated vessels at the pre-capillary and direct arterio-venous communications.[3] This causes right-to-left shunting of blood flow, mismatch between ventilation and perfusion, and diffusion limitations. Pulmonary features include digital clubbing, cyanosis, dyspnoea, platypnoea and orthodeoxia.[3]

Impaired arterial oxygenation is a hallmark of HPS. Mild hypoxaemia is a frequent feature of chronic liver disease; it occurs in approximately one-third of all patients. By contrast, severe hypoxaemia (PaO_2 < 60 mmHg) is less common with cirrhosis alone and is usually without associated cardiopulmonary disease. In the absence of independent lung disease, severe hypoxaemia in the setting of liver disease suggests the possibility of HPS.[4]

From a physiological viewpoint, HPS provides an excellent model for clinical research in the pathophysiology of pulmonary gas exchange. So far it has been possible to show that arterial hypoxaemia in this condition is (1) partitioned into components resulting from ventilation–perfusion (VA/Q) mismatching, intrapulmonary shunt and limitations of oxygen diffusion; (2) modulated by the interplay between the intrapulmonary and the extrapulmonary determinants of PaO_2, such as cardiac output and minute ventilation; (3) vulnerable to the influence of inadequate pulmonary vascular tone, and (4) resolved when the injured liver is replaced and hepatic function is restored to within normal limits.[4]

Contrast-enhanced echocardiography is considered to be standard in the diagnosis of HPS. In subjects with normal pulmonary vasculature, microtubules become lodged in the pulmonary circulation and are absorbed. The appearance of microtubules in the left side of the heart indicates right–left shunts, while bubbles that appear in the left heart immediately after they have appeared in the right atrium are suggestive of an intracardiac shunt.[5,6]

Conclusion

A high clinical suspicion of right-to-left interatrial shunts and HPS should be considered in the setting of unexplained hypoxia, especially with associated platypnoea and or orthodeoxia.

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Case Report

Single coronary artery from the right coronary sinus with proximal origin of the left anterior descending coronary artery and left circumflex as distal continuation of the right coronary artery: a rare variant

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Abstract

A single coronary artery is a rare coronary anomaly. A 68-year-old male underwent coronary angiography for recent inferior wall myocardial infarction. It revealed a common coronary trunk arising from the right sinus of Valsalva and bifurcated into the right coronary artery (RCA) and anterior descending coronary arteries. The RCA, after its usual distribution in the right atrioventricular groove, continued as the left circumflex artery in the left atrioventricular groove. There were significant stenoses in the mid and distal RCA, which were treated percutaneously.

Keywords: single coronary artery, left anterior descending artery, left circumflex artery, right coronary artery, percutaneous coronary intervention

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Coronary artery anomalies are found in 0.6 to 1.5% of coronary angiograms and are usually incidental findings.[1] Here we describe a patient with an unusual variant of a single coronary artery (SCA), who underwent successful percutaneous coronary intervention.

Case report

A diabetic 65-year-old gentleman with dyslipidaemia presented to us with a history of recent myocardial infarction. Cardiac examination was normal and a baseline electrocardiogram showed QS complexes and T-wave inversions in the inferior leads.

The echocardiogram revealed wall motion abnormalities in the right coronary artery (RCA) distribution. On invasive angiogram, a diminutive coronary artery originated from the left sinus of Valsalva and followed the course of the first diagonal branch (D) of the left anterior descending coronary artery (LAD) (Fig. 1A). A common coronary trunk was seen to arise from the right sinus of Valsalva, which bifurcated into the LAD and RCA immediately distal to the origin (Fig. 1B, C). The LAD followed a septal course beneath the right ventricular infundibulum into the anterior interventricular groove.

The RCA continued in the right atrio-ventricular groove (AVG) to produce a small posterior descending artery at the crux. Thereafter, it continued in the left AVG as the left circumflex

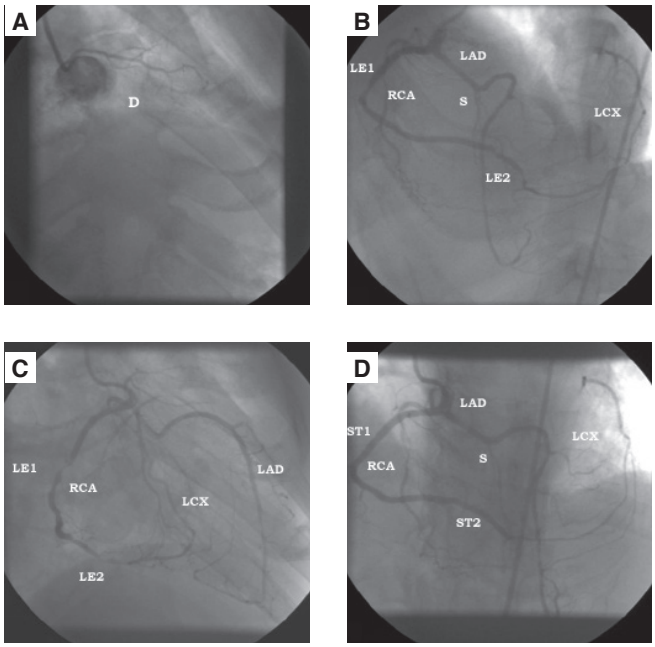

Fig. 1. A. Selective left coronary angiogram showing a diminutive artery in the diagonal (D) distribution. B. Selective angiogram of the right-sided common coronary trunk in the left anterior oblique view, showing early branching into the right coronary artery (RCA) and left anterior descending coronary artery. The distal RCA continues as the left circumflex artery. There are stenotic lesions in the mid and distal RCA. C. Selective angiogram of the right-sided common coronary trunk in the right anterior oblique view showing similar features. D. Post-intervention angiogram in the cranial antero-posterior view showing the excellent final result. LAD, left anterior descending coronary artery; LCX, left circumflex artery; ST, stent; S, septal branch; LE, lesion.

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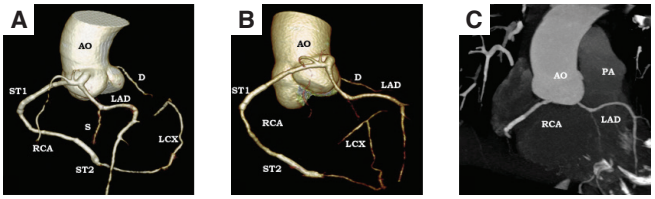

Fig. 2. A. Three-dimensional VRT image (left anterior oblique view) showing the diagonal artery from the left coronary sinus and a common coronary trunk from the right coronary sinus dividing into the right coronary artery (RCA) and left anterior descending coronary artery. The distal RCA continues as the left circumflex artery. The stents are *in situ*. B. Three-dimensional VRT image (right anterior oblique view) demonstrating similar features. C. Thick MIP image revealing the septal course of the left anterior descending artery. LAD, left anterior descending coronary artery; LCX, left circumflex artery; ST, stent; D, diagonal artery; S, septal branch.

coronary artery (LCX), supplying the posterolateral aspect of the left ventricle. There was 80% stenosis in the mid segment and two 80% tandem lesions in the distal segment of the RCA.

The patient underwent percutaneous coronary angioplasty with stenting in the mid and distal RCA, using two drug-eluting stents in the same operation (Fig. 1D). The procedure was uneventful. Later the septal course was confirmed by computed tomographic angiogram (Fig. 2A, B, C). Even though there were two coronary ostia in our patient, the entire heart was essentially supplied by the right coronary system.

Discussion

Single coronary artery is a rare coronary anomaly in structurally normal hearts, with a reported prevalence of 0.024% in the general population.[2] It accounts for less than 3% of all major coronary anomalies.[1]

Angiographically, Lipton *et al*.[2] classified SCA into various types depending on its origin, branching pattern and course of the anomalous vessel. In single coronary arteries arising from the right coronary sinus, the left system often arises either from the distal RCA after its usual distribution (R-I) or as a single artery (left main coronary artery, R-II), or two separate arteries (LAD and LCX, R-III) from the proximal part of the common trunk. A single coronary system with direct origin of the LAD from the proximal RCA and direct continuation of the circumflex from the terminal RCA is very rare.

Although an anomalous LAD arising from the right coronary artery can follow any of the four courses: septal, anterior free wall, retro-aortic and interarterial, it often follows one of the former two courses. The septal course is largely benign and no case of sudden cardiac death has yet been attributed to it.[3, 4]

Percutaneous coronary intervention is a viable therapeutic option for a single anomalous coronary artery. However, the operator should be aware of the potential risk of complications and the limitations of the procedure, as vessel compromise during angioplasty will have an impact on all three territories.[5] The distal location of the stenoses in the RCA placed our patient at a slightly lower risk for percutaneous coronary intervention.

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Case Report

A young patient with coronary artery anomaly, whose left anterior descending artery originated from the pulmonary artery, underwent cardiac arrest

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Abstract

A rare congenital anomaly of the coronary arteries, in which the left coronary arterial system starts from the arteria pulmonalis, is known as Bland–White–Garland (BWG) syndrome. Isolated left anterior descending (LAD) or circumflex (Cx) arteries originating from the pulmonary artery are even more rare. These anomalies may cause myocardial ischaemia, myocardial infarction, arrhythmia and sudden death. Even if the patient is asymptomatic, he/she should undergo corrective surgery. Here we present the case of an 18-year-old male who survived sudden cardiac arrest during exercise. We identified intra-myocardial blood flow from transthoracic echocardiography, and performed coronary and computed tomographic (CT) angiography, which showed that all the coronary arteries were ectatic and curly and there were disseminated collaterals among the coronary arteries. We diagnosed 'anomalous left coronary artery from the pulmonary artery' (ALCAPA) syndrome, as additionally, the LAD originated from the pulmonary artery. We treated the patient with a left internal mammarian artery – left anterior descending artery (LIMA–LAD) graft.

Keywords: coronary artery anomalies, echocardiography, angiography, surgical treatment

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Bland–White–Garland (BWG) syndrome is a rare congenital coronary artery anomaly in which the left coronary arterial system originates from the arteria pulmonalis. Isolated left anterior descending (LAD) or circumflex (Cx) arteries originating from the pulmonary artery are even more rare.[1] These anomalies may cause myocardial ischaemia, myocardial infarction, arrhythmia and sudden death.

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Case report

An 18-year-old male experienced sudden cardiac arrest during exercise at school. Cardiopulmonary resuscitation was performed and he was immediately revived. He was hospitalised and at first cranial pathology was suspected but a cerebral CT scan was normal. The patient was referred to our clinic with an early diagnosis of hypertrophic cardiomyopathy.

He did not have any irregularities in his history. His heart rate was 74 beats per minute, and blood pressure was 110/70 mmHg. All other examination findings were normal. Electrocardiography (ECG) revealed a sinus rhythm and T-wave negativity in the derivation of V_1–V_2. His blood analyses were normal. Holter ECG examination showed a large ORS tachycardia attack at a rate of five beats/137 per minute.

Transthoracic echocardiography (TTE) revealed a dilated left ventricle (left ventricular diastolic diameter = 58 mm, systolic diameter = 38 mm) and eccentric left ventricular hypertrophy with a normal ejection fraction. Colour flow transthoracic Doppler echocardiography (TTE) demonstrated blood flow in the myocardial wall, and the parasternal short-axis view showed abnormal flow towards the pulmonary artery, 1–2 cm below the pulmonary valve (Fig. 1A, B, C).

Upon suspicion of a coronary artery anomaly, coronary and CT coronary angiography were performed. The ostium of the LAD artery was not seen in the coronary angiography. It showed that the right coronary artery was dilated and tortuous, and it provided extensive collaterals to the LAD artery, which drained into the main pulmonary artery. Pulmonary angiography showed that the left system originated from the pulmonary artery (Fig. 2).

CT coronary angiography confirmed that the LAD artery originated from the main pulmonary artery (Fig. 3). Cardiac magnetic resonance imaging (MRI) demonstrated left ventricular hypertrophy and a sub-endocardial infarct in the apical anterior and anteroseptal zones.

Surgical correction was planned. The LAD was detached from the pulmonary artery and connected to the aorta, and the left internal mammarian artery (LIMA) was anastomosed to the LAD artery (Fig. 4).

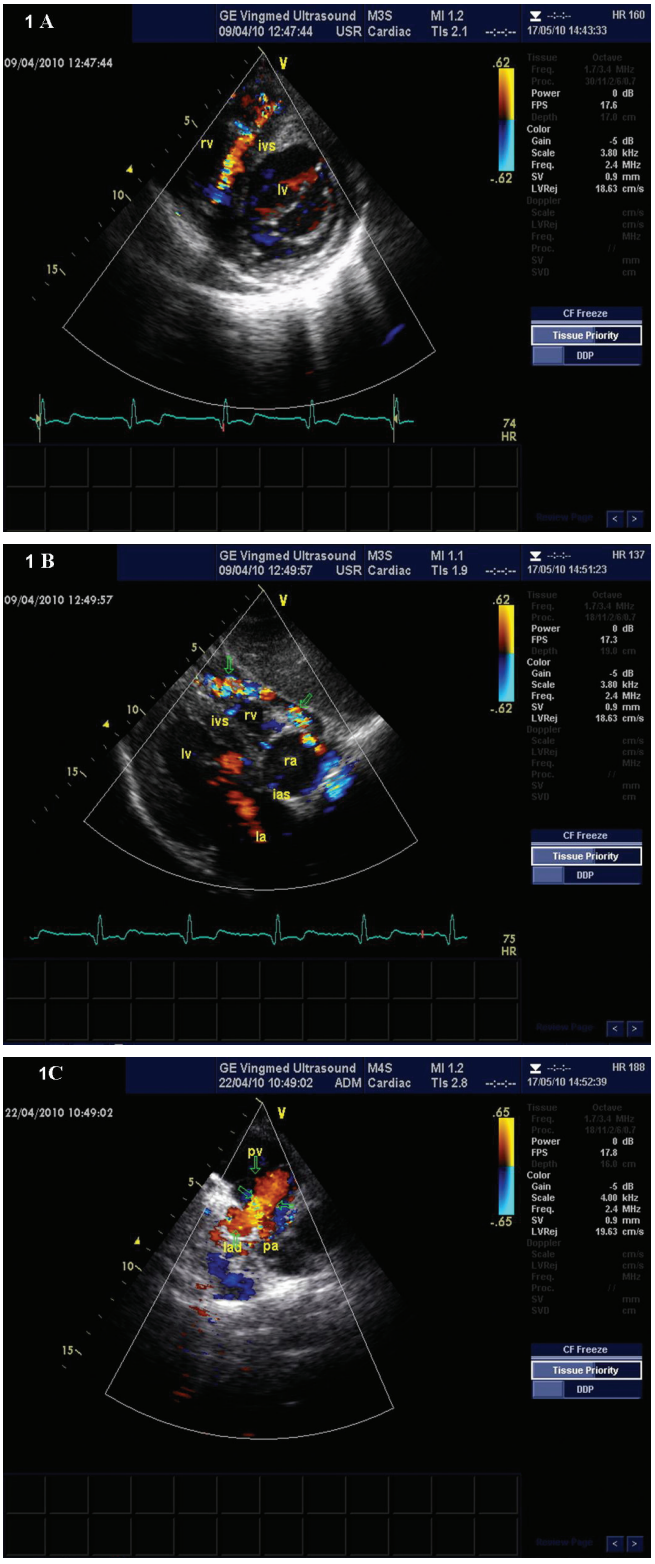

Fig. 1. In TTE with colour Doppler, the parasternal short-axis view shows abnormal blood flow through the interventricular septum (A); the subcostal view shows abnormal blood flow patterns through the free wall of the right ventricle (B); the modified parasternal short-axis view shows retrograde flow from the LAD into the pulmonary artery and LAD orifice (C). Lv: left ventricle, rv: right ventricle, la: left atrium, ra: right atrium, ivs: interventricular septum, ias: interatrial septum. pv: pulmonary valve, pa: pulmonary artery, lad: left anterior descending artery.

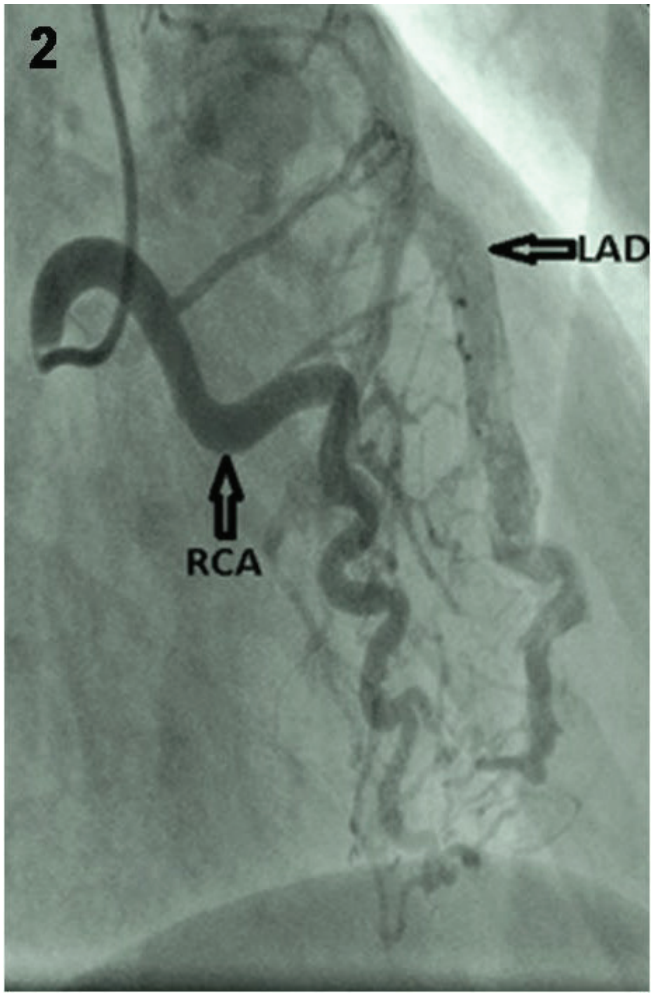

Fig. 2. Selective right coronary angiography showing the right coronary artery is ectatic and curly and the LAD is retrogradely filled with collaterals from the RCA. RCA: right coronary artery, LAD: left anterior descending artery.

Discussion

The incidence of BWG syndrome is reported as one in 300 000 live births and it accounts for only 0.24 to 0.46% of all congenital heart anomalies.[2] From the second month of life, as the vascular resistance drops in the pulmonary vascular bed, pulmonary pressure starts to decline as well. The ductus arteriosus closes and flow from the left coronary artery reverses, which reduces the perfusion pressure of the ectopic left coronary artery.

Insufficient blood supply and disturbed myocardial perfusion may lead to the development of collateral circulation between the right and left coronary arteries. If a well-developed collateral circulation is present in these patients, both the perfusion pressure and oxygen requirement of the myocardium can be met to a certain extent. This collateral circulation determines both the area of myocardial ischaemia and whether symptoms will develop. If good collateral circulation develops in these patients, it is termed adult type and if not, it is infantile type.[3]

While adult patients can be completely asymptomatic, they may present with angina, dyspnoea, syncope, myocardial infarction, arrhythmia or sudden cardiac death. Sudden cardiac death secondary to malignant ventricular arrhythmias is the most common clinical presentation in adult patients.[4]

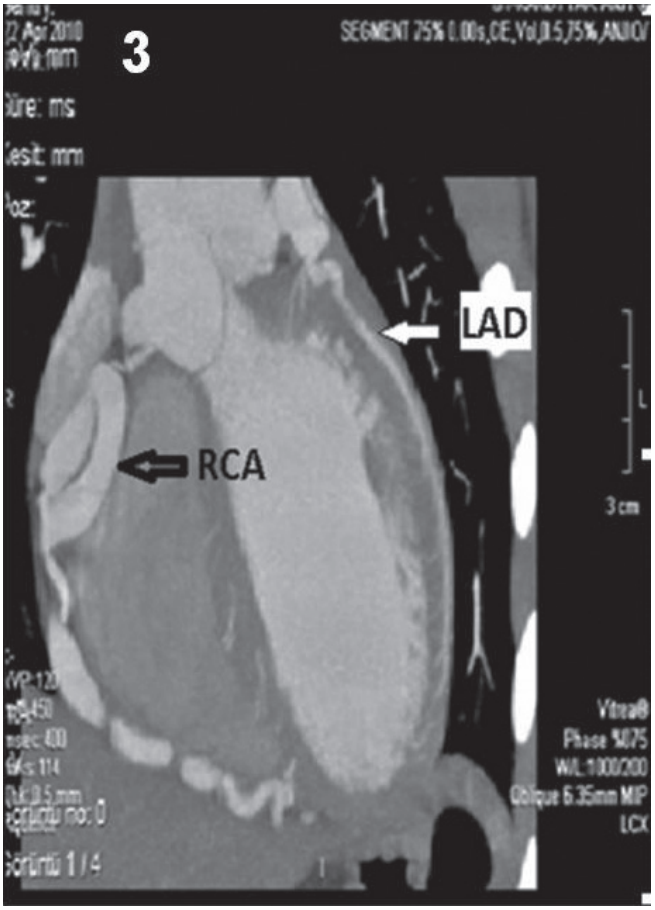

Fig. 3. Longitudinal image with CT angiography showing the right coronary artery originating from the aorta, and the LAD originating from the pulmonary artery. RCA: right coronary artery, LAD: left anterior descending artery.

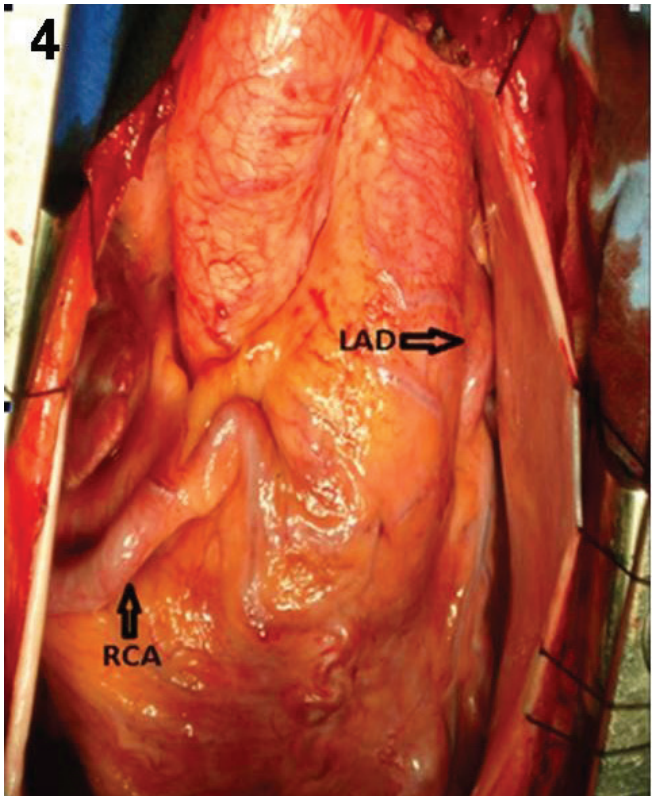

Fig. 4. After the pericardium was opened during surgery, the RCA was seen to be ectatic and curly, similar to the coronary angiographic image. The LAD was ectatic and collaterals ran between it and the RCA. RCA: right coronary artery, LAD: left anterior descending artery.

The anomaly in which the isolated LAD originates from the pulmonary artery is more rare than the classic ALCAPA syndrome. In this type of coronary artery anomaly, ischaemic risk is constituted by the low perfusion pressure in the LAD region. The right coronary and circumflex arteries may also be highly ectasic and send collaterals to the LAD.[5]

In this anomaly, the only symptom may be atypical angina, and systolic murmur can only be detected in a physical examination. Neither was present in our case, however, sudden cardiac arrest developed during exercise and cardiopulmonary resuscitation was performed. The patient had developed ventricular fibrillation, was defibrillated and returned to sinus rhythm.

In the ALCAPA syndrome, while there may be changes in the ECG such as left ventricular hypertrophy, left electrical axis deviation, and anterolateral wall infarction, the ECG may be also entirely within normal limits.[6] In our case, the ECG was in sinus rhythm and had a T-wave negativity in V_1–V_2 derivation.

The diagnosis of coronary artery anomalies with TTE is difficult because it may not always be possible to show the origins of the coronary arteries in adult patients; it is easier in newborns. In some cases, the anomalous origin of the left coronary system as well as the retrograde flow into the pulmonary artery may be seen directly.[7] If there is a strong clinical or echocardiographic-based suspicion about the existence of this anomaly, then coronary or CT angiography should definitely be performed.

In our case, we could not reach an exact diagnosis with TTE, as only an increase in the left ventricular wall thickness and slight expansion in the left ventricle were detected. However, colour Doppler examination showed intra-myocardial blood flow with a retrograde flow inside the pulmonary artery, which we had not expected.

We suspected there might be a coronary artery anomaly in the patient and performed coronary and CT angiography. The sensitivity of an angiography may be limited in the diagnosis of an anomalous coronary artery due to its invasive nature. CT angiography is a valuable non-invasive method to show abnormal coronary arteries, their origins and projections, and it indicates a prognosis of the coronary arteries.[8]

Due to the coronary steal phenomenon that occurs during exercise, arrhythmias can be triggered because of inadequate myocardial perfusion. In our case, ECG and TTE did not indicate previous myocardial infarction. There was no increase in troponin I values; however, in the cardiac MRI, we identified a sub-endocardial infarct in the apical and antero-septal regions, which we had not been able to identify with TTE. Left ventricular dysfunction, significant mitral regurgitation and pulmonary hypertension were not present in our case. However, cardiac arrest had developed during exercise.

In patients with ALCAPA syndrome, even if the patient is asymptomatic, or when ventricular arrhythmia and significant left-to-right shunt or risk of death is not present, surgical treatment is suggested.[9] In the past, several methods such as binding of the pulmonary artery or aorto-pulmonary anastomosis have been used in the treatment of ALCAPA syndrome in the elderly.

The objective in modern surgery is the formation of two coronary artery systems to ensure long-term vascular patency, using native blood vessels in order for the coronary ostia and coronary arteries to maintain their normal growth potentials. A few surgical procedures are suggested based on the localisation of the abnormal coronary artery ostium. One of these is the ligation of the abnormal coronary artery, combined with saphenous vein or LIMA graft or re-implantation to the aortic root either directly or with the help of a pulmonary flap. Another method, defined by Takeuchi,[10] involves formation of a tunnel with intra-pulmonary baffle.

Surgical treatment is also required in isolated LAD anomalies, although the ischaemic area is smaller. Direct implantation of the abnormal coronary artery to the aorta can be successfully achieved in the early stages of life; however, this type of surgical procedure is difficult and involves increased risks in older patients. Similar surgical procedures can be performed in cases of isolated LAD anomaly. With early diagnosis and surgical treatment, this syndrome usually has a good prognosis.

Isolated LAD originating from the pulmonary artery is extremely rare. The patient had exercised regularly and had never experienced any previous symptoms. However, cardiac arrest developed during exercise, he developed ventricular fibrillation and was defibrillated. The patient was referred to us for implantable cardioverter defibrillator (ICD) implantation with an early diagnosis of hypertrophic cardiomyopathy,

Anti-arrhythmia treatment must be considered for patients with a history of VT/VF (ventricular fibrillation) that is not associated with an acute ischaemic event. Treatment options include drug therapy, ICD implantation or catheter ablation. ICD implantation has been shown to be superior to drug treatment in patients with a history of VT/VF and previous myocardial infarction (secondary prophylaxis). ICD implantation may also be considered in patients without a history of arrhythmias, when there is marked left ventricular dysfunction, and electrophysiological study shows inducible VT (primary prophylaxis).[11] In our case, we implanted an ICD as secondary prophylaxis.

Conclusion

In young patients who survive sudden cardiac arrest, along with cardiomyopathy and arrhythmic events, coronary artery anomalies should be considered as a priority in establishing a diagnosis. If a strong suspicion emerges based on colour Doppler echocardiography results, the condition should be assessed with coronary artery or CT angiography.

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S4 **CRESTOR® 5 (Tablet)** Each CRESTOR® 5 tablet contains 5 mg of rosuvastatin as rosuvastatin calcium. S4 **CRESTOR® 10 (Tablet)** Each CRESTOR® 10 tablet contains 10 mg of rosuvastatin as rosuvastatin calcium. S4 **CRESTOR® 20 (Tablet)** Each CRESTOR® 20 tablet contains 20 mg of rosuvastatin as rosuvastatin calcium. S4 **CRESTOR® 40 (Tablet)** Each CRESTOR® 40 tablet contains 40 mg of rosuvastatin as rosuvastatin calcium. **PHARMACOLOGICAL CLASSIFICATION:** A. 7.5 Serum-cholesterol reducers **INDICATIONS:** Primary hypercholesterolaemia, mixed dyslipidaemia and isolated hypertriglyceridaemia (including Fredrickson Type IIa, IIb and IV; and heterozygous familial hypercholesterolaemia) as an adjunct to diet when response to diet and exercise is inadequate. Indicated in patients with homozygous familial hypercholesterolaemia, either alone or as an adjunct to diet and other lipid lowering treatments. CRESTOR® 40 mg should only be considered in patients with severe hypercholesterolaemia and high cardiovascular risk who do not achieve their treatment goal on 20 mg of CRESTOR® or alternative therapy. Specialist supervision is recommended when the 40 mg dose is initiated. **REGISTRATION NUMBERS:** CRESTOR® 5: 41/7.5/0298, CRESTOR® 10: 36/7.5/0349, CRESTOR® 20: 36/7.5/0350, CRESTOR® 40: 36/7.5/0351. **DETAILS OF THE REGISTERED LICENCE HOLDER:** AstraZeneca Pharmaceuticals (Pty) Ltd Reg No. 1992/005854/07. No. 5 Leeuwkop Road, Sunninghill, 2157, South Africa. Tel: 011 797 6000. Fax: 011 797 6001. www.astrazeneca.co.za. For full details relating to any information mentioned above please refer to the package insert of CRESTOR® 5 mg, 10 mg, 20 mg and 40 mg. CRESTOR® is a registered trademark of AstraZeneca group of companies. Licensed from Shionogi & Co Ltd, Osaka, Japan. EPI Date: 12/03/2008. Expiry Date: May 2014.

References: 1. CRESTOR® package insert **2.** Jones P, Davidson MH, Stein EA, *et al.* Comparison of the Efficacy and Safety of Rosuvastatin Versus Atorvastatin, Simvastatin, and Pravastatin Across Doses (STELLAR* Trial). *Am J Cardiol* 2003;**92**:152-160. **3.** Schuster H, Barter PJ, Stender S, *et al.* Effects of switching statins on achievement of lipid goals. Measuring Effective Reduction in Cholesterol Using Rosuvastatin Therapy (MERCURY I) study. *Am Heart J* 2004;**147**:705-712. **4.** Rosenson RS. Statins: can the new generation make an impresssion? *Expert Opin Emerg Drugs* 2004;**9**(2):269-279. **5.** Shepherd J, Hunninghake DB, Stein EA, *et al.* Safety of rosuvaststin. *Am J Cardiol* 2004;**94**:882-888.

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1. Weidmann P. Metabolic profile of indapamide sustained-release in patients with hypertension. Drug Safety 2001;24(15):1155-1165.
2. Department of Health website *http://www.doh.gov.za* – Accessed 11/06/2012.

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